Baffled by benzenes? Confused by carboxylic acids?
Here's the help you need — in plain English!

Organic Chemistry I

FOR

DUMMIES®



Arthur Winter
Creator, Organic Chemistry Help!
Web site at chemhelper.com

A Reference for the Rest of Us!®



FREE eTips at dummies.com®

Get Smart at Dummies.com

Dummies.com makes your life easier with 1,000s of answers on everything from removing wallpaper to using the latest version of Windows.

Check out our

- Videos
- Illustrated Articles
- Step-by-Step Instructions

Plus, each month you can win valuable prizes by entering our Dummies.com sweepstakes.*

Want a weekly dose of Dummies? Sign up for Newsletters on

- Digital Photography
- Microsoft Windows & Office
- Personal Finance & Investing
- Health & Wellness
- Computing, iPods & Cell Phones
- eBay
- Internet
- Food, Home & Garden

Find out "HOW" at Dummies.com

*Sweepstakes not currently available in all countries; visit Dummies.com for official rules.

Organic Chemistry I FOR DUMMIES®

by Arthur Winter



John Wiley & Sons, Inc.

Organic Chemistry I For Dummies®
Published by
John Wiley & Sons, Inc.
111 River St.
Hoboken, NJ 07030-5774
www.wiley.com

Copyright © 2005 by John Wiley & Sons, Inc., Hoboken, New Jersey

Published by John Wiley & Sons, Inc., Hoboken, New Jersey

Published simultaneously in Canada

No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording, scanning, or otherwise, except as permitted under Sections 107 or 108 of the 1976 United States Copyright Act, without either the prior written permission of the Publisher, or authorization through payment of the appropriate per-copy fee to the Copyright Clearance Center, 222 Rosewood Drive, Danvers, MA 01923, 978-750-8400, fax 978-646-8600. Requests to the Publisher for permission should be addressed to the Permissions Department, John Wiley & Sons, Inc., 111 River Street, Hoboken, NJ 07030, 201-748-6011, fax 201-748-6008, or online at http://www.wiley.com/go/permissions.

Trademarks: Wiley, the Wiley Publishing logo, For Dummies, the Dummies Man logo, A Reference for the Rest of Us!, The Dummies Way, Dummies Daily, The Fun and Easy Way, Dummies.com and related trade dress are trademarks or registered trademarks of John Wiley & Sons, Inc. and/or its affiliates in the United States and other countries, and may not be used without written permission. All other trademarks are the property of their respective owners. Wiley Publishing, Inc., is not associated with any product or vendor mentioned in this book.

LIMIT OF LIABILITY/DISCLAIMER OF WARRANTY: THE PUBLISHER AND THE AUTHOR MAKE NO REPRESENTATIONS OR WARRANTIES WITH RESPECT TO THE ACCURACY OR COMPLETENESS OF THE CONTENTS OF THIS WORK AND SPECIFICALLY DISCLAIM ALL WARRANTIES, INCLUDING WITHOUT LIMITATION WARRANTIES OF FITNESS FOR A PARTICULAR PURPOSE. NO WARRANTY MAY BE CREATED OR EXTENDED BY SALES OR PROMOTIONAL MATERIALS. THE ADVICE AND STRATEGIES CONTAINED HEREIN MAY NOT BE SUITABLE FOR EVERY SITUATION. THIS WORK IS SOLD WITH THE UNDERSTANDING THAT THE PUBLISHER IS NOT ENGAGED IN RENDERING LEGAL, ACCOUNTING, OR OTHER PROFESSIONAL SERVICES. IF PROFESSIONAL ASSISTANCE IS REQUIRED, THE SERVICES OF A COMPETENT PROFESSIONAL PERSON SHOULD BE SOUGHT. NEITHER THE PUBLISHER NOR THE AUTHOR SHALL BE LIABLE FOR DAMAGES ARISING HEREFROM. THE FACT THAT AN ORGANIZATION OR WEBSITE IS REFERRED TO IN THIS WORK AS A CITATION AND/OR A POTENTIAL SOURCE OF FURTHER INFORMATION DOES NOT MEAN THAT THE AUTHOR OR THE PUBLISHER ENDORSES THE INFORMATION THE ORGANIZATION OR WEB SITE MAY PROVIDE OR RECOMMENDATIONS IT MAY MAKE. FURTHER, READERS SHOULD BE AWARE THAT INTERNET WEB SITES LISTED IN THIS WORK MAY HAVE CHANGED OR DISAPPEARED BETWEEN WHEN THIS WORK WAS WRITTEN AND WHEN IT IS READ.

For general information on our other products and services, please contact our Customer Care Department within the U.S. at 877-762-2974, outside the U.S. at 317-572-3993, or fax 317-572-4002.

For technical support, please visit www.wiley.com/techsupport.

Wiley publishes in a variety of print and electronic formats and by print-on-demand. Some material included with standard print versions of this book may not be included in e-books or in print-on-demand. If this book refers to media such as a CD or DVD that is not included in the version you purchased, you may download this material at http://booksupport.wiley.com. For more information about Wiley products, visit www.wiley.com.

Library of Congress Control Number: 2005923194

ISBN 978-0-7645-6902-9 (pbk); ISBN 978-0-470-38934-8 (ebk)

Manufactured in the United States of America

15 14 13

1B/RV/QV/QW/IN



About the Author

Arthur Winter is a graduate of Frostburg State University (located in the mountains of western Maryland), where he received his BS in chemistry. Currently, he is a fourth-year doctoral student in organic chemistry at the University of Maryland in College Park, where his research involves studying extremely short-lived reactive intermediates (<0.000001 second lifetimes) using laser spectroscopy. He likes helping students with their struggles with organic chemistry and is the creator of `www.chemhelper.com`, an organic chemistry help Web site.

In summers, Arthur is an avid trout fisherman and huntsman of dangerous or delicious animals; in winters, he hibernates. Year-round, he likes watching violent movies, drinking sugar-saturated tea solutions, and reading trashy fiction. He enjoys competitive weight lifting, iron man competitions, lumberjacking, and jousting — from the comfort of a couch in front of his TV. He often boasts of his ability to make minute rice in thirty seconds (admittedly, somewhat *al dente*) and is the proud owner of a collection of inexpensive watches. He's a good whistler, a bad loser, and tasteless joke enthusiast. He currently resides in College Park, Maryland.

Dedication

To Don Weser, an inspiring teacher and a giant in the field of chemical education (if not also in real life).

Author's Acknowledgments

I thank the team at Wiley who helped put this book together. Particularly, I thank acquisitions editor, Kathy Cox, who got the ball rolling on this project; my copy editor, Dr. Janet Dunn, who made countless improvements to the manuscript; and my patient project editor, Tere Stouffer, who oversaw the book's creation. I also thank the technical reviewer, Dr. Carl Johnson, who helped eliminate factual errors, and the Wiley graphics department for rendering the many images in this book.

I thank Jonathan and Julian Winter for their support, and Brian Price, Mary Mumper, Robert Larivee, Fred Senese, Glynn Baugher, and Dan Falvey for providing a first-class education.

Publisher's Acknowledgments

We're proud of this book; please send us your comments through our Dummies online registration form located at www.dummies.com/register/.

Some of the people who helped bring this book to market include the following:

Acquisitions, Editorial, and Media Development

Project Editor: Tere Stouffer

Acquisitions Editor: Kathy Cox

Copy Editor: Janet S. Dunn, PhD

Technical Reviewer: Carl Johnson, PhD

Editorial Manager: Michelle Hacker

Editorial Supervisor: Carmen Krikorian

Editorial Assistant: Melissa Bennett

Cover Photos: © cosmin4000/iStockphoto

Cartoons: Rich Tennant (www.the5thwave.com)

Composition Services

Project Coordinator: Adrienne Martinez

Layout and Graphics: Jonelle Burns, Lauren Goddard, Denny Hager, Joyce Haughey, Shelley Norris, Barry Offringa, Lynsey Osborn

Proofreaders: Laura Albert, Jessica Kramer, Toni Settle

Indexer: Johnna VanHoose

Publishing and Editorial for Consumer Dummies

Kathleen Nebenhaus, Vice President and Executive Publisher

Kristin Ferguson-Wagstaffe, Product Development Director

Ensley Eikenburg, Associate Publisher, Travel

Kelly Regan, Editorial Director, Travel

Publishing for Technology Dummies

Andy Cummings, Vice President and Publisher

Composition Services

Debbie Stailey, Director of Composition Services

Contents at a Glance

Introduction 1

Part 1: Going Organic: The Chemistry of Carbon 9

Chapter 1: The Wonderful World of Organic Chemistry 11
Chapter 2: Dissecting Atoms: Atomic Structure and Bonding 19
Chapter 3: Speaking with Pictures: Drawing Structures 41
Chapter 4: Covering the Bases (And the Acids) 65
Chapter 5: Reactivity Centers: Functional Groups 77
Chapter 6: Seeing in 3-D: Stereochemistry 93

Part II: Hydrocarbons 111

Chapter 7: The Bones of Organic Molecules: The Alkanes 113
Chapter 8: Seeing Double: The Alkenes 141
Chapter 9: It Takes Alkynes: The Carbon-Carbon Triple Bond 169

Part III: Functional Groups 177

Chapter 10: Replacing and Removing: Substitution and Elimination Reactions 179
Chapter 11: Getting Drunk on Organic Molecules: The Alcohols 195
Chapter 12: Side-By-Side: Conjugated Alkenes and the Diels-Alder Reaction 205
Chapter 13: Lord of the Rings: Aromatic Compounds 215

Part IV: Spectroscopy and Structure Determination 247

Chapter 14: A Smashing Time: Mass Spectrometry 249
Chapter 15: Seeing Good Vibrations: IR Spectroscopy 267
Chapter 16: NMR Spectroscopy: Hold on to Your Hats, You're Going Nuclear! 279
Chapter 17: Following the Clues: Solving Problems in NMR 301

Part V: The Part of Tens 321

Chapter 18: Ten Keys for Surviving Orgo 323
Chapter 19: Ten Cool Organic Discoveries 329
Chapter 20: Ten Great Organic Chemists 337

Part VI: Appendixes 343
Appendix A: Working Multistep Synthesis Problems 345
Appendix B: Working Reaction Mechanisms 353
Appendix C: Glossary 361
Index 373

Table of Contents

Introduction 1

About This Book 2
Conventions Used in This Book 3
Foolish Assumptions 3
How This Book Is Organized 4
Part I: Going Organic: The Chemistry of Carbon 4
Part II: Hydrocarbons 5
Part III: Functional Groups 5
Part IV: Spectroscopy and Structure Determination 6
Part V: The Part of Tens 6
Part VI: Appendixes 6
Icons Used in This Book 6
Where to Go from Here 7

Part 1: Going Organic: The Chemistry of Carbon 9

Chapter 1: The Wonderful World of Organic Chemistry 11

Shaking Hands with Organic Chemistry 11
What Are Organic Molecules, Exactly? 13
An Organic Chemist by Any Other Name 14
Synthetic organic chemist 15
Bioorganic chemist 15
Natural products chemist 16
Physical organic chemist 17
Organometallic chemist 17
Computational chemist 17
Materials chemist 18

Chapter 2: Dissecting Atoms: Atomic Structure and Bonding 19

Electron House-Arrest: Shells and Orbitals 20
Electron apartments: Orbitals 21
Electron instruction manual: Electron configuration 23
Atom Marriage: Bonding 24
To Share or Not to Share: Ionic and Covalent Bonding 25
Mine! They're all mine! Ionic bonding 25
The name's Bond, Covalent Bond 27
Electron piggishness and electronegativity 27

Separating Charge: Dipole Moments 29
Problem solving: Predicting bond dipole moments 30
Problem solving: Predicting molecule dipole moments 31
Seeing Molecular Geometries 32
Mixing things up: Hybrid orbitals 33
Predicting hybridization for atoms 35
It's All Greek to Me: Sigma and Pi Bonding 36

Chapter 3: Speaking with Pictures: Drawing Structures 41

Picture-Talk: Lewis Structures 43
Taking charge: Assigning formal charges 43
Drawing structures 45
Atom packing: Condensed structures 46
Structural shorthand: Line-bond structures 47
Converting Lewis structures to line-bond structures 48
Determining the number of hydrogens on line-bond structures 49
So lonely: Determining lone pairs on atoms 51
Problem Solving: Arrow Pushing 51
Drawing Resonance Structures 53
Rules for resonance structures 54
Problem solving: Drawing resonance structures 56
Drawing more than two resonance structures 59
Assigning importance to resonance structures 60
Common mistakes in drawing resonance structures 62

Chapter 4: Covering the Bases (And the Acids) 65

A Defining Moment: Acid-Base Definitions 66
Arrhenius acids and bases: A little watery 66
Pulling for protons: Brønsted acids and bases 67
Electron lovers and haters: Lewis acids and bases 68
Comparing Acidities of Organic Molecules 69
Comparing atoms 70
Seeing atom hybridization 71
Seeing electronegativity effects 72
Seeing resonance effects 72
Defining pKa: A Quantitative Scale of Acidity 73
Problem Solving: Predicting the Direction of Acid-Base Reactions at Equilibrium 74

Chapter 5: Reactivity Centers: Functional Groups 77

Hydrocarbons 78
Double the fun: The alkenes 78
Alkynes of fun 80
Smelly compounds: The aromatics 81

Singly Bonded Heteroatoms 82
Happy halides 82
For rubbing and drinking: Alcohols 84
What stinks? Thiols 85
How ethereal 85
Carbonyl Compounds 86
Living on the edge: Aldehydes 86
Stuck in the middle: Ketones 87
Carboxylic acids 89
Sweet-smelling compounds: Esters 89
Nitrogen-containing functional groups 90
I am what I amide 90
Be nice, don't be amine person 91
Nitriles 91
Test Your Knowledge 91

Chapter 6: Seeing in 3-D: Stereochemistry 93

Drawing Molecules in 3-D 94
Comparing Stereoisomers and Constitutional Isomers 94
Mirror Image Molecules: Enantiomers 95
Seeing Chiral Centers 96
Assigning Configurations to Chiral Centers: The R/S Nomenclature 97
Problem Solving: Determining R/S Configuration 98
Step 1: Prioritizing the substituents 98
Step 2: Putting the number-four substituent in the back 99
Step 3: Drawing the curve 100
The Consequences of Symmetry: Meso Compounds 101
Rotating Plane-Polarized Light 103
Multiple Chiral Centers: Diastereomers 104
Representing 3-D Structures on Paper: Fischer Projections 105
Rules for using Fischer projections 105
Determining R/S configuration from a Fischer projection 106
Seeing stereoisomerism with Fischer projections 107
Spotting meso compounds with Fischer projections 108
Keeping the Jargon Straight 108

Part II: Hydrocarbons 111

Chapter 7: The Bones of Organic Molecules: The Alkanes 113

What's in a Name? Alkane Nomenclature 113
All in a line: Straight-chain alkanes 114
Reaching out: Branching alkanes 115
More than one-of-a-kind 118
Naming complex substituents 119

Converting a Name to a Structure....120
Problem Solving: Drawing Isomers from a Molecular Formula....123
Step 1....123
Step 2....123
Step 3....125
Step 4....125
Step 5....126
Conformation of Straight-Chain Alkanes....126
Newman! Conformational analysis and Newman projections....127
Conformations of butane....128
Full Circle: Cycloalkanes....130
Stereochemistry of cycloalkanes....131
Conformations of cyclohexane....131
Problem Solving: Drawing the Most Stable Chair Conformation....134
Reacting Alkanes: Free Radical Halogenation....136
Getting things started: Initiation....136
Keeping the reaction going: Propagation....137
You're fired: Termination steps....137
Selectivity of chlorination and bromination....139

Chapter 8: Seeing Double: The Alkenes....141

Defining Alkenes....142
Taking Away Hydrogens: Degrees of Unsaturation....143
Determining degrees of unsaturation from a structure....144
Problem solving: Determining degrees of unsaturation from a molecular formula....145
Nomenclature of alkenes....146
Numbering the parent chain....146
Adding multiple double bonds....148
Common names of alkenes....148
Stereochemistry of alkenes....149
Same side or opposite sides? Cis and trans stereochemistry....149
Playing a game of high-low: E/Z stereochemistry....150
Stabilities of Alkenes....152
Alkene substitution....152
Stability of cis and trans isomers....152
Formation of Alkenes....153
Elimination of acid: Dehydrohalogenation....153
Losing water: Dehydration of alcohols....154
Alkenes from coupling: The Wittig reaction....154
Reactions of Alkenes....156
Adding hydrohalic acids across double bonds....156
I'm positive: Carbocations....157
Adding water across double bonds....161
Double the fun: Bromination....164

Chopping up double bonds: Ozonolysis 165
Double-bond cleavage: Permanganate oxidation 165
Making cyclopropanes with carbenes 166
Making cyclopropanes: The Simmons-Smith reaction 167
Making epoxides 167
Adding hydrogen: Hydrogenation 168

Chapter 9: It Takes Alkynes: The Carbon-Carbon Triple Bond 169

Naming Alkynes 169
Seeing Alkyne Orbitals 170
Alkynes in Rings 171
Making Alkynes 171
Losing two: Dehydrohalogenation 172
Coupling alkynes: Acetylide chemistry 172
Brominating alkynes: Double the fun 173
Saturating alkynes with hydrogen 174
Adding one hydrogen molecule to alkynes 174
Oxymercuration of alkynes 175
Hydroboration of alkynes 176

Part III: Functional Groups 177

Chapter 10: Replacing and Removing: Substitution and Elimination Reactions 179

Group Swap: Substitution Reactions 179
Seeing Second-Order Substitution: The S_N2 Mechanism 180
How fast? The rate equation for the S_N2 reaction 181
Effect of the substrate on the S_N2 reaction 182
Needs nucleus: The role of the nucleophile 183
Seeing the S_N2 reaction in 3-D: Steroechemistry 185
Seeing solvents effects 185
I'm outta here: The leaving group 186
First-Order Substitution: The S_N1 Reaction 187
How fast? The rate equation for the S_N1 reaction 187
Seeing good S_N1 substrates 189
Seeing solvent effects on the S_N1 reaction 190
Stereochemistry of the S_N1 reaction 190
Other fun facts about the S_N1 reaction 191
Seeing Elimination Reactions 192
Seeing second-order eliminations: The E2 reaction 192
Seeing first-order elimination: The E1 reaction 193
Help! Distinguishing Substitution from Elimination 193

Chapter 11: Getting Drunk on Organic Molecules: The Alcohols . . . 195

Classifying Alcohols 195
An Alcohol By Any Other Name: Naming Alcohols 196
Alcohol-Making Reactions 198
Adding water across double bonds 198
Reduction of carbonyl compounds 198
The Grignard reaction 200
Reactions of Alcohols 201
Losing water: Dehydration 201
Making ethers: Williamson ether synthesis 202
Oxidation of alcohols 202

Chapter 12: Side-By-Side: Conjugated Alkenes and the Diels-Alder Reaction 205

Seeing Conjugated Double Bonds 205
Addition of Hydrohalic Acids to Conjugated Alkenes 206
Seeing the reaction diagram of conjugate addition 207
Comparing kinetics and thermodynamics of conjugate addition 209
The Diels-Alder Reaction 209
Seeing the diene and the dienophile 210
Stereochemistry of addition 211
Seeing bicyclic products 211
Problem Solving: Determining Products of Diels-Alder Reaction 212

Chapter 13: Lord of the Rings: Aromatic Compounds 215

Defining Aromatic Compounds 216
Structure of benzene 216
Diversity of aromatic compounds 217
So what exactly makes a molecule aromatic? 218
Hückel's $4n + 2$ rule 218
Explaining Aromaticity: Molecular Orbital Theory 219
What the heck is molecular orbital theory? 220
Making MO diagrams 220
Two rings diverged in a wood: Frost circles 221
Making the MO diagram of benzene 221
Seeing the MOs of benzene 222
Making the MO diagram of cyclobutadiene 224
Problem Solving: Determining Aromaticity 225
Problem Solving: Predicting Acidities and Basicities 228
Comparing acidities 228
Comparing basicities 229
Naming Benzenes and Aromatics 230
Common names of substituted benzenes 231
Names of common aromatics 232

Bringing Out the Howitzers: Electrophilic Aromatic Substitution of Benzene 232
Adding alkyl substituents: Friedel-Crafts alkylation 233
Overcoming adversity: Friedel-Crafts acylation 235
Reducing nitro groups 235
Oxidation of alkylated benzenes 236
Adding Two: Synthesis of Disubstituted Benzenes 236
Electron donors: Ortho-Para activators 238
Electron-withdrawing groups: Meta directors 238
Problem Solving: Synthesis of Substituted Benzenes 241
Nucleophiles Attack! Nucleophilic Aromatic Substitution 243

Part IV: Spectroscopy and Structure Determination 247

Chapter 14: A Smashing Time: Mass Spectrometry 249

Defining Mass Spectrometry 250
Taking Apart a Mass Spectrometer 250
The inlet 251
Electron ionization: The smasher 251
The sorter and weigher 252
Detector and spectrum 253
The Mass Spectrum 254
Kind and Caring: Sensitivity of Mass Spec 255
Resolving the Problem: Resolution 255
Changing the Weight: Isotopes 256
The Nitrogen Rule 258
Identifying Common Fragmentation Patterns 258
Smashing alkanes 259
Breaking next to a heteroatom: Alpha cleavage 259
Loss of water: Alcohols 260
Rearranging carbonyls: McLafferty Rearrangement 261
Breaking benzenes and double bonds 261
Self test: Working the problem 262
Key Ideas Checklist 264

Chapter 15: Seeing Good Vibrations: IR Spectroscopy 267

Bond Calisthenics: Infrared Absorption 268
Applying Hooke's law to molecules 268
Seeing bond vibration and IR light absorption 269
Seeing absorption intensity 270
IR forbidden stretches 271
Dissecting an IR Spectrum 271
Identifying the Functional Groups 273
Sizing up the IR spectrum 273
Recognizing functional groups 274

Seeing to the Left of the C-H Absorptions 275
Big and fat: The alcohols 276
Milking the spectrum: Amines 276
Seeing to the Right of the C–H Absorptions 276
Big and tall: Carbonyl groups 276
Hydrocarbon stretches: Alkenes, alkynes, and aromatics 277

Chapter 16: NMR Spectroscopy: Hold on to Your Hats, You're Going Nuclear! 279

Why NMR? 280
How NMR Works 281
Giant magnets and molecules: NMR theory 281
Grab your jackets: Electron shielding 284
The NMR Spectrum 284
Standardizing chemical shifts 285
Seeing symmetry and chemical equivalency 286
The NMR Spectrum Manual: Dissecting the Pieces 287
Seeing the chemical shift 288
Incorporating the integration 290
Catching on to coupling 291
Considering Carbon NMR 296
Checklist: Putting the Pieces Together 298

Chapter 17: Following the Clues: Solving Problems in NMR 301

Follow the Clues 302
Clue 1: Determine the degrees of unsaturation (DOU) from the molecular formula 303
Clue 2: Look at the IR spectrum to determine the major functional groups present in the unknown compound 303
Clue 3: Determine the peak ratios by measuring the heights of the integration curves 304
Clue 4: Break the NMR peaks into fragments using the integration from Clue 3 306
Clue 5: Combine the fragments in a way that fits with the NMR peak splitting, the chemical shift, and the degrees of unsaturation 307
Clue 6: Recheck your structure with the NMR and the IR to make sure it's an exact match 308
Working Problems 309
Example 1: Using the molecular formula and NMR to deduce the structure of a molecule 310
Example 2: Using the molecular formula, IR, and NMR to deduce the structure of a molecule 315

Three Common Mistakes in NMR Problem Solving 318
Mistake 1: Trying to determine a structure from the chemical shift 319
Mistake 2: Starting with coupling 319
Mistake 3: Confusing integration with coupling 320

Part V: The Part of Tens 321

Chapter 18: Ten Keys for Surviving Orgo 323

Have a Good Attitude 323
Work the Problems 323
Don't Fall Behind 324
Study the Right Way 325
Go to Class 326
Get Help When You Need It 326
Ask Questions 327
Do Organic Every Day 327
Take Exams the Right Way 328
Work the Problems 328

Chapter 19: Ten Cool Organic Discoveries 329

Explosives and Dynamite! 329
Fermentation 330
The Synthesis of Urea 330
The Handedness of Tartaric Acid 331
Diels-Alder Reaction 331
Buckyballs 332
Soap 333
Aspartame 333
Penicillin 334
Teflon 334

Chapter 20: Ten Great Organic Chemists 337

Robert Burns Woodward 337
August Kekulé 338
K.C. Nicolaou 338
E. J. Corey 339
Louis Pasteur 340
Dorothy Hodgkin 340
Emil Fischer 340
Linus Pauling 341
John Pople 341
Friedrich Wöhler and Adolf Kolbe 342

Part VI: Appendixes *343*

Appendix A: Working Multistep Synthesis Problems **345**

Why Multistep Synthesis? 345
The Five Commandments 347
Commandment 1: Thou shalt learn thy reactions 348
Commandment 2: Thou shalt compare carbon skeletons 348
Commandment 3: Thou shalt work backward 349
Commandment 4: Thou shalt check thyne answer 351
Commandment 5: Thou shalt work many problems 351

Appendix B: Working Reaction Mechanisms **353**

The Two Unspoken Mechanism Types 353
Do's and Don'ts for Working Mechanisms 354
Types of Mechanisms 356
Seeing by Example: Example Mechanism Problem 357

Appendix C: Glossary **361**

Index *373*

Introduction

Regrettably, when many people think of chemicals, the first things that usually pop into their minds are substances of a disagreeable nature — harmful pesticides and chemical pollutants, nerve agents and chemical weapons, or carcinogens and toxins.

But most chemicals play roles of a more positive nature. For example, both water and sugar are chemicals. Why are these chemicals important? Well, for one thing, both are components of beer. The enzymes in yeasts are also important chemicals used in fermentation, a process that involves the breaking down of starches into beer. Ethyl alcohol is the all-important chemical responsible for beer's effect on the body. I hope that these three representative examples of chemicals have thoroughly rebutted the notion that all chemicals are bad!

In fact, those who have a bad opinion of all chemicals must suffer from the psychological condition of self-loathing, because human bodies are essentially large vats of chemicals. Your skin is made up of chemicals — along with your heart, lungs, kidneys, and all of your other favorite organs and appendages. And most of the chemicals in your body — in addition to the chemicals in all other living things — are not just any kinds of chemicals, but are organic chemicals. So, anyone who has any interest at all in the machinery of living things (or in the chemistry of beer and wine) will have to deal at some point and at some level with organic chemistry.

Of course, the natures of these dealings have historically not always been so pleasant. Pre-med students and bio majors (and even chemistry majors) have butted heads with organic chemistry for decades, and, regrettably, the winner of this duel has not always been the human.

Part of the problem, I think, comes from students' preconceptions of organic chemistry. I admit that, like many students, I had the worst preconceptions going into organic chemistry. When I thought of organic class, I thought of wearying trivia about the chemical elements, coma-inducing lectures delivered in a monotone, complex mathematical equations sprawling across mile-long chalkboards, and a cannon fire of structures and chemical reactions vomited one after the other in succession. The only successful students, I thought, would be those wearing thick spectacles, periodic-table ties, and imitation leather shoes with Velcro straps.

But if my preconceptions of organic lecture were bad, my preconceptions of organic labs were worse. I feared the organic laboratory course, certain the instant I would step into the lab, all the chemicals would instantly vaporize, condense on my unclothed extremities, and permeate my hair, pores, follicles, and nails. As a result, my skin would erupt in a rash and slough off in dry flakes. I would be bald. My nails would yellow. The love of my life would take one look at my scarred physiognomy, sicken of men, and leave me sitting alone, Job-like, amongst the ashes of my existence, scratching my weeping sores with a broken potsherd.

Okay, so I was wrong on that one. I was surprised to find that I actually liked organic chemistry. I really liked doing it; it was fun. And working in the laboratory making new substances was less toxic than I thought it would be and was instead interesting and even entertaining. I was wrong about the math, too: If you can count to 11 without taking off your shoes then you can do the math in organic chemistry. The turning point, really, was when I stopped fighting organic chemistry, stopped feeding my preconceptions, and changed my attitude. That was the point that I really started enjoying the subject.

I hope you choose not to fight organic chemistry from the beginning (as I did) and instead decide to just get along and become friends with organic (but just friends; you don't want to let things get out of hand here). In that case, this book will help you get to know organic chemistry as quickly as possible (and as well as possible), so that when your professor decides to test you on how well you know your new-found comrade, you'll do just fine.

About This Book

With *Organic Chemistry I For Dummies,* I've written the book that I would have wanted when I was taking the first semester of organic chemistry. That means that the book is very practical. This book doesn't try to mimic a textbook, or try to replace it. Instead, it's designed as a complement to a text, highlighting the most important concepts in your textbook. While a textbook gives you mostly a "just-the-facts-ma'am" style of coverage of the material — and provides you with lots of problems at the end of chapters to see if you can apply those facts — this book acts as an interpreter, translator, and guide to the fundamental concepts in the subject. This book also gets to the nuts and bolts of how to actually go about tackling certain problems in organic chemistry.

Tackling the problems is where the majority of students have the most trouble, in part because so many aspects of a problem must be considered. Where's the best place to start a problem? What should you be on the lookout for? What interesting features (that is, sneaky tricks) do professors like to slip into problems, and what's the best strategy for tackling a particular problem type? I answer some of these questions in this book. While this book cannot possibly

show you how to solve every kind of problem that you encounter in organic chemistry, it does provide guides for areas that, in my experience, are the usual problem areas for students. These guides include the main trouble spots of resonance, stereochemistry, mechanisms, synthesis, and spectroscopy.

Beyond the problem types covered, these guides should give you insight into how to logically go about solving problems in organic chemistry. They show you how to rationally organize your thoughts and illustrate the kind of thinking you need to perform when approaching new problems in organic chemistry. In this way, you see how to swim instead of just panicking after being shoved abruptly into the deep end of the pool.

Additionally, I make clear the most important underlying principles in organic chemistry. I use familiar and easy-to-understand language, along with a great many clarifying analogies, to make palatable the hard concepts and technical jargon that comes with the territory. While this book is designed for students taking a first-semester course in introductory organic chemistry, it should also be a solid primer for those who want to understand the subject independently of a course.

And if you can understand the concepts in organic chemistry, and you can work the problems, then you can reasonably say that the world is your oyster because you have conquered introductory organic chemistry. And that's no small feat!

Conventions Used in This Book

Throughout this book, I use the term "organic-speak" to indicate the jargon of the organic chemist. Most often, this jargon (like all self-respecting jargon) can intimidate and confuse the uninitiated, and can unclarify, obfuscate, and disilluminate the topic in question. I tell you what the jargon means in understandable terms.

Foolish Assumptions

In this book, I assume that you've had at least some chemistry in the past, and that you're familiar with the basic principles of chemistry. For example, I assume that you're familiar with the Periodic Table (see the Cheat Sheet at the front of this book), that you understand what atoms are and what they're made up of (neutrons, protons, and electrons), and that you have some knowledge of bonding and chemical reactions. You should also know about kinetics (like rate equations and rate constants) and chemical equilibria. If

you've had a two-semester course in general chemistry, that's perfect. (If you feel that your general chemistry is a bit rusty, I review in Chapter 2 the most important concepts that you need to know for organic chemistry.)

Another assumption I make is that you're reading this book in order to understand the critical concepts in organic chemistry, and, in particular, that you're interested in figuring out how to solve problems in organic chemistry (because problems make up a great deal of the questions on exams). That assumption means that — for the sake of having a book shorter than *Moby Dick* — a lot of the details covered in a textbook are not covered here, and coverage instead is given to the fundamentals.

Also, I assume that you're looking for a book that's written in an accessible, easy-to-understand, conversational style, free of a lot of the jargon and stuffiness of academic writing. Or perhaps you just aren't that great at chemistry, and want a helpful reference that will guide you through the rough spots and make the subject more enjoyable (or less painful, depending on your point of view).

How This Book Is Organized

I've organized the book into six major parts, and each of the parts is further subdivided into chapters. I've organized the book in a way that follows along with the basic organization of most undergraduate textbooks (although each of them organizes the material a little bit differently). If you choose, then, you can follow this book in a roughly straight-through fashion with your textbook, using it as a practical guide of the textbook material. Additionally, every chapter in this book is modular, which means that you can start reading at any point without feeling lost.

At the end of the book are the appendixes that include tips on how to work reaction mechanisms and tackle multistep syntheses. Like any of the chapters in this book, these sections are modular, and can be referred to without having read previous chapters as a requirement.

Part 1: Going Organic: The Chemistry of Carbon

In this part, I introduce you to the world of organic chemistry. I define organic chemistry, discuss what makes a molecule organic, and talk about what organic chemists do all day long (besides lining their pocket protectors with inexpensive pens). I also review the essentials of bonding, orbitals, and electron configuration.

Here I introduce the language of organic chemistry, which is one of pictures and structures rather than one of words. I incorporate the different ways organic chemists communicate using structures (from full Lewis structures to condensed structures and line-bond structures) and show you how to draw each of these structures correctly. I also give you a guide for drawing the despised resonance structures, which are used by organic chemists to confuse students (and, as some would argue, to correct for a flaw in depicting the location of certain electrons in Lewis structures).

Because almost *all* organic reactions are acid-base reactions, I cover the important aspects of acid and base chemistry, and show you how to predict the relative acid and base strengths qualitatively. Additionally, because the functional groups (or reactive centers) contained in a molecule predict the molecule's reactivity, I introduce all of the major classes of compounds that you need to know right at the beginning of this book.

This part is the warm-up pitch, the icebreaker, the handshake.

Part II: Hydrocarbons

In this part, I discuss organic molecules that only contain the elements of hydrogen and carbon — that is, the hydrocarbons! Hydrocarbons are the bones of organic molecules, and include the alkanes (molecules with only singly bonded hydrogen and carbon atoms), the alkenes (molecules with carbon-carbon double bonds), and the alkynes (molecules with carbon-carbon triple bonds). Here I introduce the nomenclature of organic molecules, and I discuss the chemical reactions that these molecules undergo.

In this part of the book, I also introduce the concept of *conformation,* or the different ways molecules can bend and flex, in addition to the concept of stereochemistry, or the way bonds are oriented in three dimensions. I also show you how organic molecules can double back on each other to form rings, and you see whether I have the self-control to restrain myself from making a cheap *Lord of the Rings* pun (don't bet on it).

Part III: Functional Groups

If the hydrocarbons (and particularly the alkanes) are the bones of organic molecules, then the functional groups are the muscles that get things moving. Functional groups are the reactive centers in molecules. Some of the most important functional groups include the alcohols, the halides, and the aromatic compounds. I cover these functional groups in detail in this part, and I show you the properties and reactions of these functional groups.

Additionally, I get to the stereochemistry of organic molecules — the way that atoms are arranged in three-dimensional space — and show you how the stereochemistry of molecules is important in biological systems.

Part IV: Spectroscopy and Structure Determination

How do you determine the structure of a compound when given a nondescript white powder? How do you know that you got the right product from your reaction? In this part, I show you how organic chemists determine the structures of molecules using an instrumental technique called spectroscopy (a technique that measures how light interacts with molecules), and mass spectrometry (a process involving the smashing of molecules into tiny pieces and weighing all of the little bits). I show you how you can use clues from these structure-determining techniques to piece together the structure of an unknown compound.

Part V: The Part of Tens

The parts of ten are lists of ten items that relate to organic chemistry. I've included ten great guys and gals in organic, ten cool organic discoveries, and ten tips for passing orgo.

Part VI: Appendixes

In these appendixes, I include guides for solving mechanism problems and multistep synthesis problems. These guides will be helpful after you begin to understand chemical reactions of organic compounds. Additionally, I include a chemical glossary to help keep you straight on the jargon of the organic chemist.

Icons Used in This Book

The icons are the helpful little pictures in the margins. I use them to give you a heads-up about the coverage of the material. I include the following icons in this book:



I use this icon when giving time-saving pointers.

I double dip with this icon. I use this icon not only to jog your memory of something that you should have learned previously, but also for really important concepts that you should remember.

I use this icon to warn you of a chemical or technique that may be particularly dangerous. I also use it to warn you of common traps that students can fall into when tackling certain problems.

I try to avoid getting too technical, so you won't see this icon very much. When this icon is used, it indicates a discussion of a concept that's a little more in-depth (which you can skip if you want to).

to Go from Here

In short, from here you can go anywhere you want. All of the chapters in this book are designed to be modular, so you can hop-scotch around, reading the chapters in any order you find most suitable. Perhaps you're having trouble with a particular concept, like drawing resonance structures or solving for structures using NMR spectroscopy. In that case, skip straight to the chapter that deals with that particular topic. Or, if you want, you can read the book straight through, using it as a kind of interpreter and guide to the textbook.

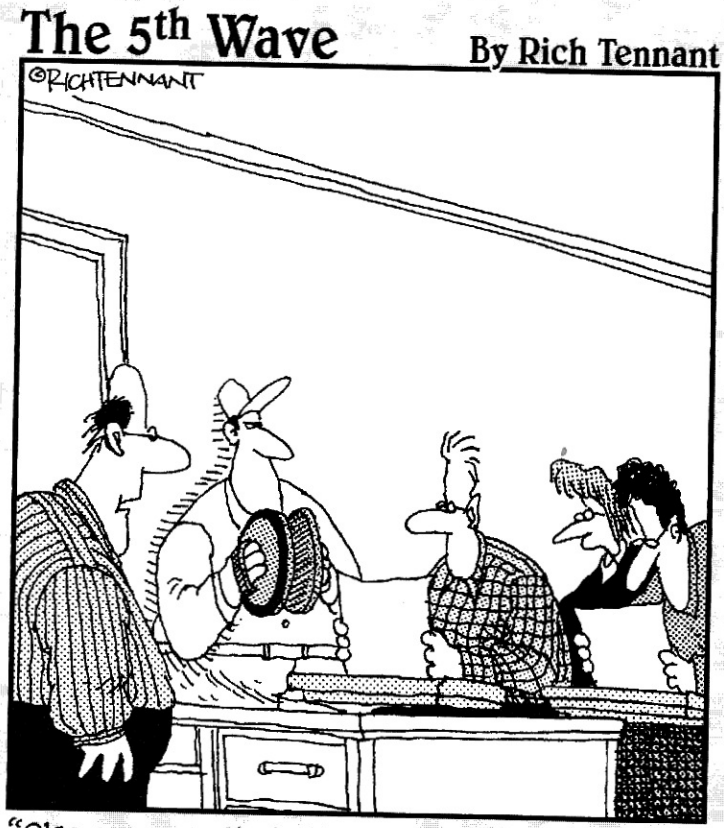
If you get the gist of what organic is all about, and have a solid background in the critical concepts in general chemistry — like electron configuration, orbitals, and bonding — you may wish to skip the first two chapters and dive right into Chapter 3, which explains how organic structures are drawn. Or you may want to just skim the first couple of chapters as a quick introduction and memory refresher (summer vacations have a strange way of wiping your memory slate sparkly clean, particularly in the area of chemistry).

Keep in mind that the appendixes at the end of the book contain valuable guides for working multistep synthesis problems and proposing reasonable reaction mechanisms, in addition to a chemical glossary. Multistep synthesis and reaction mechanism problems show up very often on exams in organic chemistry (except, perhaps, at the very beginning), so you may want to check those out when your instructor introduces chemical reactions (the timing of this inevitable event varies from course to course). Particularly useful at the beginning of the course may be the "Ten Keys for Surviving Orgo" found in Part V, the Part of Tens.

This book is yours, so use it in any way you think will help you the most.

Part I

Going Organic: The Chemistry of Carbon



"Okay – now that the paramedic is here with the defibrillator and smelling salts, prepare to open your test booklets..."

In this part . . .

Organic compounds are ubiquitous in nature. You find them in living things, you find them in the atmosphere you breathe, you find them in the foods you eat, and you find them in the clothes you wear. In short, you can't escape organic molecules. In this part, I introduce you to organic compounds, tell you what makes an organic compound organic, show you how to draw organic molecules, and discuss how organic molecules are put together.

Chapter 1

The Wonderful World of Organic Chemistry

▶ Breaking down the mysteries of carbon

Organic chemistry is a tyrant you've heard about a lot. You've heard your acquaintances whisper about it in secret. It's mean, they say; it's brutish and impossibly difficult; it's unpleasant to be around (and smells sort of funny). This is the chapter where I introduce you to organic chemistry, and where, I hope, you decide to forget about all of the negative comments you've heard about the subject.

In this chapter, I show you that the nasty rumors about organic chemistry are untrue (mostly). I also talk about what organic chemistry is, and why you should spend precious hours of your life studying it. I show you that discovering organic chemistry really is a worthwhile and enjoyable expedition. And the journey is not all uphill, either.

Hands with Organic Chemistry

Although organic is a very important and valuable subject, and for some it's even a highly enjoyable subject, I realize that organic chemistry is intimidating, especially when you first approach it. Perhaps you've already had what many old-timers refer to simply as The Experience, the one where you picked up the textbook for the first time. This is the time when you heaved the book

off the shelf in the bookstore. When you strained your back trying to hold it aloft. When you felt The Dread creep down your spine as you scanned through the book's seemingly infinite number of pages and feared that, not only would you have to read all of it, but that reading it wouldn't be exactly like breezing through a Hardy Boys adventure or a Nancy Drew mystery.

No doubt, the material appeared strange. Opening to a page halfway through the book you saw bizarre chemical structures littering the page, curved arrows swooshing here and there like flocks of starlings, and data tables bulging with an inordinate number of values — values that you suspect you might be required to memorize. I admit that organic is a little frightening.

The soap opera of organic molecules

Organic molecules govern our life processes like metabolism, genetic coding, and energy storage. In nature, organic molecules also play out a crazy soap opera, acting as the medium for many twists and turns, deceptions, betrayals, strategic alliances, romances, and even warfare.

Take plants, for example. They seem so defenseless. When a predator comes to lunch on a plant's leaves, the plant can't just pack up its bags and take off. It's stuck where it is, so there's nothing it can do, right? But although plants may seem defenseless, they're not. Many plants produce *antifeedants*, nasty organic compounds that are unpleasant tasting or even toxic to those who would dare eat them. (As a kid, I always *knew* Brussels sprouts contained something like this.) Predators that have feasted on a plant rich in these unpleasant compounds make sure to refrain from eating them in the future.

To produce antifeedants to discourage being eaten is bad enough, but sometimes plants have defenses that seem just plain evil. Certain species of plants, for example, can detect when a caterpillar has decided to munch on its leaves (by detecting organic molecules present in the caterpillar's spit!). When the plant detects that a caterpillar has decided to make supper on its leaves, the plant emits volatile organic molecules into the air, chemicals designed to attract wasps. When the wasps buzz by to check out what's up, they see the caterpillars eating the plant and killing it. The wasps couldn't care less about the misfortunes of the plant, but the female wasps do need a comfortable spot to hatch their eggs. And what's a snugger nursery than the innards of a fat, juicy caterpillar?

When a wasp spots a caterpillar, it swoops down, makes a crash landing on the caterpillar's back, stings the caterpillar into paralysis, and lays its eggs *inside* of it! When the wasp larvae hatch shortly thereafter, they make the caterpillar their first meal, munching on it contentedly from the inside out. The wasp has now reproduced and has had its little offspring fed, and the plant is rid of its pest — a strange alliance between wasp and plant, all thanks to communication by organic molecules. And that's just one episode in this never-ending soap opera, produced, funded, and sponsored by organic molecules.

I think most students feel this way before they take this class, and probably even your professor did, as did her professor before her. *So you're not alone.* But you can take comfort in knowing that organic chemistry is not as hard as it looks. Those who put in the required amount of work — which, admittedly, is a lot — and don't fall behind, almost always do well. (You might want to check out Chapter 18 for some helpful tips on how to pass orgo.) More than almost any other subject, organic chemistry rewards the hard workers (like you), and relentlessly punishes the slothful (the others in your class). I think understanding organic chemistry is not so much hard as it is hard work.



I hope all this talk about how intimidating the course is hasn't put a damper on your enthusiasm, because the subject of organic chemistry really is a doozy. To learn about organic chemistry is to learn about life itself, because living organisms are composed of organic molecules and use organic molecules to function. Swarms of organic molecules are at work in your body — fueling your brain, helping your neurons fire, and getting the muscles in your mouth to clench open and shut — and that's just a small sampling of the organic molecules needed in order for you to complain about your school's chemistry requirements.

Humans, in fact, are composed almost entirely of organic molecules (all the soft parts anyway), from the muscles, hair, and organs, to the fats that cushion bellies and keep you toasty warm during sweltering summer nights (some are more richly blessed in this regard than others). Organic molecules can also range in size from the very tiny, like the carbon dioxide you exhale that consists of only three atoms, to the staggeringly large, like DNA, which acts as your molecular instruction manual and is made up of millions of atoms.

What Are Organic Molecules, Exactly?

But what ties all of these molecules together? *What exactly makes a molecule organic?* The answer lies in a single, precious atom: carbon. All organic molecules contain carbon, and to study organic chemistry is to study molecules made of carbon and to see what kinds of reactions they undergo and how they're put together. When these principles are known, that knowledge can be put to good use, to make better drugs (the legal ones, I hope), stronger plastics, better materials to make smaller and faster computer chips, better paints, dyes, coatings, and polymers, and a million other things that help to improve our quality of life.

That said, I should also point out that the field of organic chemistry is essentially an arbitrary one, that the same fundamental laws of chemistry that apply to inorganic molecules apply just as well to organic ones. This connectivity of

the branches of chemistry is actually a relatively new idea, as organic molecules were once falsely thought to have a "vital life force" that other molecules didn't have (for more, see the section on Wöhler in Chapter 20). Despite the destruction of this theory of *vitalism,* chemists still keep the old divisions of chemistry, divisions that define the branches of physical chemistry, inorganic chemistry, and biochemistry. But these barriers are slowly beginning to dissolve, and are kept mainly to help students focus on the material taught in a given course.

It is fascinating that, of all the many elements present in the universe, living things selected carbon as their building block. What is it that makes carbon so special, so unique? What makes it better as a foundation for life than any of the other elements? What makes this atom so important that an entire subject focuses around this single atom, while the chemistry of all other elements is lumped into a big mushy pile known as inorganic chemistry? Is carbon really, in fact, all that special compared to the many other elements that could have been selected?

In short, yes. Carbon is very special, and its usefulness lies in its versatility. Carbon has the capability of forming four bonds, so molecules that contain carbon can be of varied and intricate designs. Also, carbon bonds represent the perfect trade-off between stability and reactivity — carbon bonds are neither too strong nor too weak. Instead, they epitomize what chemists refer to affectionately as the *Goldilocks principle* — carbon bonds are neither "too hot" nor "too cold," but are "just right." If these bonds were too strong, carbon would be unreactive and useless to organisms; if they were too weak, they would be unstable and would be just as worthless. Instead, carbon bonds straddle the two extremes, being neither too strong nor too weak, making them fit for being the backbone of life.

Also, carbon is one of the very few elements that can form strong bonds to itself, in addition to being able to form bonds to a wide variety of other elements. Carbon bonds can even double back to form rings (see Chapter 7). Because of this ability to bond with itself and other elements, carbon can form an incredibly vast array of molecules. Millions of organic compounds have already been made and characterized, and undoubtedly many millions more will be discovered (perhaps, dear reader, by you!).

An Organic Chemist by Any Other Name . . .

Just as the field of chemistry can be broken down into different branches, so, too, can the field of organic chemistry be broken down into specialized areas of research. Those who work in these different areas — these specialized

"organic chemists" — illustrate the diversity of the field of organic chemistry and its connection to other branches in chemistry, branches like physical chemistry, biochemistry, and inorganic chemistry.

Synthetic organic chemist

Synthetic organic chemists concern themselves with making organic molecules. In particular, synthetic chemists are interested in taking cheap and available starting materials and converting them into valuable products. Some synthetic chemists devote themselves to developing procedures that can be used by others in constructing complex molecules. These chemists want to develop general procedures that are flexible and can be used in synthesizing as many different kinds of molecules as possible. Others devote themselves to developing reactions that make certain kinds of bonds, such as carbon-carbon bonds.

Others use known procedures to tackle multistep syntheses — the making of complex compounds using many individual, known reactions. Performing these multistep syntheses tests the limits of known procedures. These multistep syntheses force innovation and creativity on the part of the chemist, in addition to encouraging endurance and flexibility when a step in the synthesis goes wrong (things inevitably go wrong during the synthesis of complex molecules). Such innovation contributes to the body of knowledge of organic chemistry.

Synthetic organic chemists often flock to the pharmaceutical industry, mapping out efficient reaction pathways to make drugs and optimizing reactions to make very complicated organic molecules as cheaply and efficiently as possible for use as pharmaceuticals. (Sometimes improving the yield of the reaction of a big-name drug by a few percentage points can save millions of dollars for a pharmaceutical company each year.) If you take a laboratory course in organic chemistry, you'll be doing a lot of organic synthesis.

Bioorganic chemist

Bioorganic chemists are particularly interested in the enzymes of living organisms. Enzymes are very large organic molecules, and are the worker bees of cells, catalyzing (speeding up) all of the reactions in the cell. These enzymes range from the moderately important ones (from the point of view of the average college student) such as the ones that keep us alive by breaking down food and storing energy, to the really important ones, like the ones in yeasts that are responsible for fermentation, or the breaking down of sugars into alcohol.

These catalysts work with an efficiency and selectivity that synthetic organic chemists can only envy (see the previous section). Bioorganic chemists are particularly interested in looking at these marvels of nature, these enzymes, and determining how they operate. When chemists understand the mechanisms of how these enzymes catalyze particular reactions in the cell, this knowledge can be used to design enzyme *inhibitors,* molecules that block the action of these enzymes.

Such inhibitors make up a great deal of the drugs on the market today. Aspirin, for example, is an inhibitor of the *cyclooxegenase (COX)* enzymes. These COX enzymes are responsible for making the pain transmitters in the body (called the *prostaglandins*). These transmitters are the messengers that tell your brain to inflict a great and mighty pain in the thumb that you just smashed with a slip of your hammer. When the aspirin drug inhibits these COX enzymes from operating, the enzymes in your body can no longer make these pain-signaling molecules. In this way, the feeling of pain in the body is reduced. Many other examples of these kinds of inhibitor drugs exist today, and these drugs are designed by bioorganic chemists.

Natural products chemist

Natural products chemists isolate compounds from living things. Organic compounds isolated from living organisms are called *natural products.* Throughout history, drugs have come from natural products. In fact, only recently have drugs been made synthetically in the lab. Penicillin, for example, is a natural product produced by a fungus, and this famous drug has saved millions of lives by killing harmful bacteria. The healing properties of herbs and teas and other "witches' brews" are usually the result of the natural products contained in the plants. Some Native American groups chewed willow bark to relieve pain, as the bark contained the active form of aspirin; other Native American groups engaged in the smoking of peyote, which contains a natural product with hallucinogenic properties. Smokers get a buzz from the natural product in tobacco called nicotine; coffee drinkers get their buzz from the natural product found in coffee beans called caffeine.

Even today, a great many of the drugs found on the shelves of pharmacies are derived from natural products. Once extracted from the living organism, natural products are often tested by chemists for biological activity. For example, a natural product might be tested to see if it can kill bacteria or cancer cells, or if it can act as an anti-inflammatory drug. Often when chemists find a "hit" — a compound that shows useful biological activity — the structures of these natural products are then modified by synthetic organic chemists to try to increase the potency of the compound or to reduce the number of harmful side effects produced by the natural product.

Physical organic chemist

Physical organic chemists are interested in understanding the underlying principles that determine why atoms behave as they do. Physical organic chemists, in particular, study the underlying principles and behaviors of organic molecules. Some physical organic chemists are interested in modeling the behavior of chemical systems and understanding the properties and reactivities of molecules. Others study and predict how fast certain reactions will occur; this specialized area is called *kinetics.* Still others study the energies of molecules, and use equations to predict how much product a reaction will make at equilibrium; this area is called *thermodynamics.* Physical organic chemists are also interested in *spectroscopy* and *photochemistry,* both of which study the interactions of light with molecules. (Photosynthesis by plants is probably the most well-known example of light interacting with molecules in nature.)

Organometallic chemist

Organometallic chemists are interested in molecules that contain both metals and carbon. Such molecules are most often used as catalysts for chemical reactions. (Catalysts speed up reactions.) Carbon-carbon bonds are strong compared to carbon-metal bonds, so these carbon-metal bonds are much more easily made and more easily broken than carbon-carbon bonds. As such, they are useful for catalyzing chemical transformations of organic molecules. Many organometallic chemists concern themselves with making and optimizing organometallic catalysts for specific kinds of reactions.

Computational chemist

With the recent advances in the speed of computers, chemists have rushed to use computers to aid their own studies of atoms and molecules. *Computational chemists* model compounds (both inorganic and organic compounds) to predict many different properties of these compounds. For example, computational chemists are often interested in the three-dimensional structure of molecules and in the energies of molecules.

The models generated by computational chemists are getting more and more sophisticated as computers increase in speed and as physical chemists create better models. Many drugs are now designed on computers by computational chemists; this process is called *in silico* drug design, meaning that the drug is designed in the silicon-based computer. Typically, drugs work by blocking a receptor on an enzyme (see the explanation for Bioorganic chemist). *In silico* drug design focuses on modeling to see which compounds would best fit into

the drug's target receptor. This allows for *rational drug design,* or the use of the brain to come up with the structure of a drug rather than simply using the "brute force methods" of the past, methods that involved testing thousands of randomly selected compounds and looking for biological activity.

Materials chemist

Materials chemists are interested in, well, materials. Plastics, polymers, coatings, paints, dyes — all of these are of interest to the materials chemist. Materials chemists often work with both organic and inorganic materials, but many of the compounds of interest to materials chemists are organic. Teflon is an organic polymeric material that keeps things from sticking to surfaces, polyvinyl chloride (PVC) is a polymer used to make pipes, and polyethylene is a plastic found in milk jugs and carpeting.

Materials chemists also design environmentally safe detergents that retain their cleaning power. Organic materials are also required for photolithography to make smaller, faster, and more reliable computer chips. All of these applications and millions of others are of interest to the materials chemist.

Chapter 2

Dissecting Atoms: Atomic Structure and Bonding

In This Chapter

- Taking apart an atom and putting it back together
- Reviewing electron apartments: orbitals
- Predicting dipole moments for bonds and molecules
- Discovering ionic and covalent bonds
- Mixing in orbital mixing
- Determining orbital pictures for organic molecules

In this chapter, you take apart an atom, study the most important pieces (being careful not to lose any), and then put it back together again, as if you were an atom mechanic. After you see all the pieces, including where they fit in an atom and how they work, you begin to see how atoms can come together and bond, and you discover the different kinds of bonds. Here, you find out that atoms were not created equally: Some atoms are greedy, and they selfishly plunder the electrons in a bond, while others are more generous. I show you how to distinguish the altruistic atoms from the swines, and how this predictor can be used to predict the separation of charge in a bond or molecule (this separation is called a *dipole*), a tool useful in understanding the reactivity of a molecule. I also dissect *orbitals* — the apartments that electrons reside in — and show how their overlap leads to bonding with other atoms.

So, prepare to get your hands greasy and have carbon grit etched under your fingernails. And don't worry about the mess.

Electron House-Arrest: Shells and Orbitals

The soul of an atom is the number of protons it has in its nucleus; this number cannot be changed without changing the identity of the atom itself. You can determine how many protons an atom has by looking at its atomic number on the Periodic Table. Your friend carbon, for example, has an atomic number of six, so it has six protons tucked away in its nucleus. Because protons are positively charged, in order for an atom to remain electrically neutral, the atom needs the same number of electrons (which are negatively charged) as it has protons.



If an atom has more or fewer electrons than it has protons — in other words, when the number of positively charged parts doesn't balance the number of negatively charged parts — the atom itself becomes charged and is called an *ion.* If an atom has more electrons than it has protons, it becomes a negatively charged ion, called an *anion* (pronounced ANN-eye-on). If it has fewer electrons than it has protons, it becomes a positively charged ion called a *cation* (pronounced CAT-eye-on).

Unlike protons, electrons are not held tightly in the nucleus of an atom, but are held in shells that surround the nucleus. In a qualitative way, you can think of the electron shells as being concentric spheres that surround the nucleus of the atom. The first shell is the closest to the nucleus of the atom, is of the lowest energy, and can hold up to two electrons. (You often see electrons abbreviated as *e–*, so using this notation, the first shell can hold 2*e–*). See Figure 2-1. The second shell is higher in energy, is farther away from the nucleus, and can hold up to eight electrons. The third shell is higher yet in energy, and can hold up to 18 electrons. I don't talk about the shells higher than the third (because you don't deal with them in organic chemistry), except to say that the higher the number of the shell, the farther it is from the nucleus, the more electrons it can hold, and the higher it is in energy.

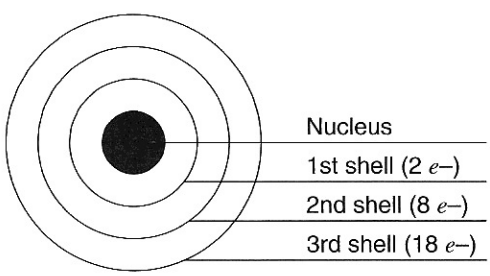


Figure 2-1: The nucleus and lower energy shells of an atom.

Electron apartments: Orbitals

Electron shells are further subdivided into *orbitals,* or the actual location in which an electron is found within the shell. Quantum mechanics — that scary subject dealing with mathematical equations too complicated to cover in organic chemistry (yay!) — says that you can never know exactly where an electron is at a given moment, but you can know the region of space in which an electron will be found, and that is the electron's orbital.

So what's the difference between a shell and an orbital? A shell indicates the energy level of a particular electron, and the orbital is the actual location in space where the electron resides. A shell that is full of electrons is spherical in shape (refer to Figure 2-1). The shell can be thought of as the floor in the apartment complex where an electron lives (the energy level), whereas the orbital is the actual apartment in which the electron resides.

You can take this analogy a step further to clarify what you know about the electron. All electrons in atoms are under house arrest; they can't be just anywhere in an atom, but are restricted to their particular orbital apartments. But quantum mechanics closes the doors and the windows to the apartment, so you can never peek in and know for sure exactly where the electron is at a given moment (this uncertainty in knowing the locations of electrons is called the *Heisenberg Uncertainty Principle*).

Although you can't know the exact location of an electron at any given moment, you can know the region in space in which an electron must be found, which is its orbital. And the shape of these apartments — these electron orbitals — becomes important in bonding. The atomic orbitals that you deal with in organic chemistry come in two kinds, the *s* orbitals and the *p* orbitals, and each kind has a distinctive shape. Drawings of these orbitals show where an electron in a particular orbital will be found 95 percent of the time. An *s* orbital is spherical in shape, whereas a *p* orbital is shaped like a dumbbell (sort of; see Figure 2-2). Each orbital can hold up to two electrons, but if there are two electrons in an orbital, they must have opposite spins. (You may have been taught that the *p* orbitals holds six electrons, but that's because there are three individual *p* orbitals in a *p* level, each of which holds two electrons.) The *spin* of an electron in an orbital is a somewhat abstract property that doesn't really have a counterpart in our big world, but you can think of these spins qualitatively as electrons spinning around the orbital like tops — one electron spins one way about the axis in the orbital, and the other spins the opposite way.

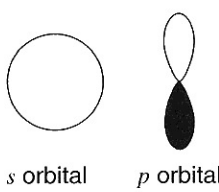


Figure 2-2: The shapes of the *s* and *p* orbitals.



Chemists also use a specific syntax when referring to orbitals. A number is placed in front of an orbital type to designate which shell that orbital resides in. For example, the 2*s* orbital refers to the *s* orbital in the second shell. If the electron occupancy of that orbital is important, the number of electrons in that orbital is placed in a superscript following the number. See Figure 2-3.

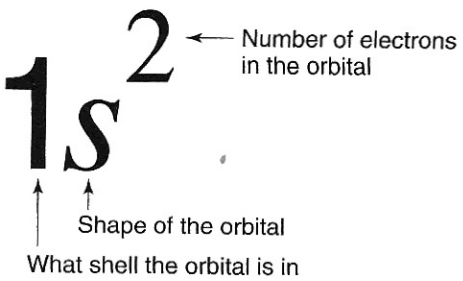


Figure 2-3: Breaking down electron configuration symbols.



Now that you know what orbitals are, you can see how the different kinds fit into the electron shells. The 1*s* orbital is spherically symmetric, holds two electrons, and is the only orbital in the first shell. The second shell contains both *s* and *p* orbitals and holds up to eight electrons. The 2*s* orbital has the same spherical shape as the 1*s* orbital, but it is larger and higher in energy. The 2*p* level consists of three individual *p* orbitals — one that points in the *x* direction (p_x), one that points in the *y* direction (p_y) and one that points in the *z* direction (p_z). Because each of these *p* orbitals are of equal energy, they are said to be *degenerate orbitals,* using organic-speak. See Figure 2-4. In general, the *p* levels can hold up to six electrons (because they have three individual *p* orbitals, each of which can hold two electrons), and the *s* levels can hold up to two electrons (because they have just one orbital that can hold up to two electrons).

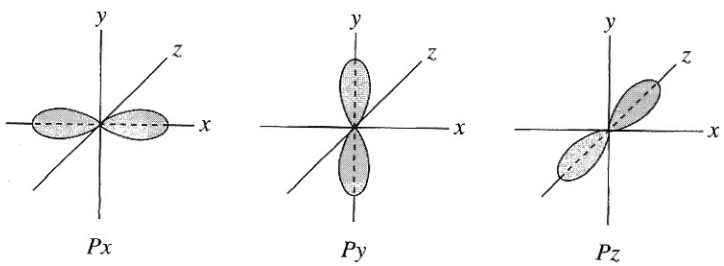


Figure 2-4: The three types of *p* orbitals.

Electron instruction manual: Electron configuration

Chemists like to know which orbitals are occupied by electrons in an atom, because where the electrons are located in an atom often predicts that atom's reactivity. To build the *ground state electron configuration,* or the list of orbitals occupied by electrons in a particular atom, you start by placing electrons into the lower energy orbitals and then build up from there. Nature, like human beings, is lazy and prefers to be in the lowest energy state possible. (For humans, laziness means sitting on the couch watching TV rather than studying organic chemistry.) The Aufbau chart in Figure 2-5 (Aufbau is the German word for *building*) is helpful for remembering which orbitals fill first. Simply follow the arrows. The lowest energy orbital is 1*s*, followed by 2*s*, 2*p*, 3*s*, 3*p*, 4*s*, and so on.

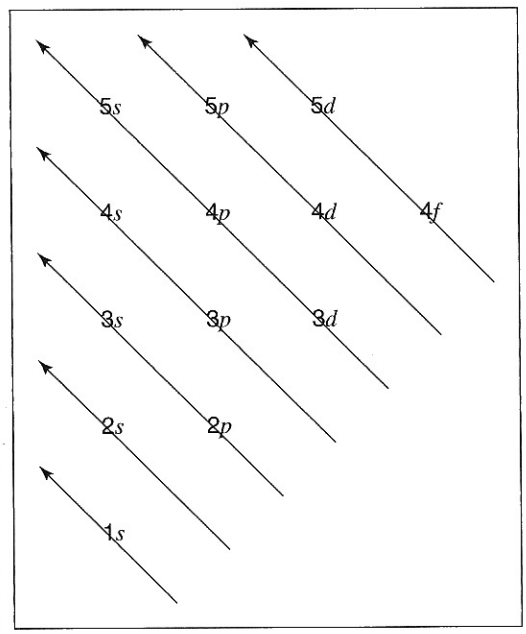


Figure 2-5: The Aufbau electron-ordering scheme.

Filling orbitals with electrons is a fairly straightforward task — you just fill two electrons per orbital, starting with the lowest energy orbitals and working up until you run out of electrons. But the last electrons you place into orbitals must sometimes be placed a little differently. *Hund's rule* tells you what to do when you come to the last of the electrons that you need to place

into orbitals, and you are at an orbital level that will not be entirely filled. In such a case, Hund's rule states that the electrons should go into different orbitals with the same spin instead of pairing up into a single orbital with opposite spin. This rule applies, in part, because electrons repel each other and want to get as far away from each other as possible and putting them into separate orbitals gets the two electrons farther away from each other.

Writing the electron configuration for an atom using Hund's rule will make more sense if you do one. Try determining the electron configuration of carbon, for example. Carbon has six electrons to put into orbitals. Because you always start by putting the electrons in the lowest energy orbitals first and building up, you put the first two electrons in the 1*s* orbital, the next two into the 2*s*, and the remaining two into the 2*p* orbitals. But because the 2*p* level can hold up to six electrons, you have to follow Hund's rule for these last two electrons and put the two electrons into different *p* orbitals with the same spin. As a result, these two electrons go into separate *p* orbitals, not the same one.

Therefore, the electron configuration of carbon is written $1s^2\,2s^2\,2p_x^{\,1}\,2p_y^{\,1}\,2p_z^{\,0}$, (not $1s^2\,2s^2\,2p_x^{\,2}\,2p_y^{\,0}\,2p_z^{\,0}$, which violates Hund's rule).

Atom Marriage: Bonding

Now that you know how electrons fit into atoms, you can see how atoms can come together and bond. But first, why do atoms make bonds? Aren't atoms happy by themselves? Aren't carbons happy with their carboniness, fluorines with their fluorininess, sodiums with their sodiuminess? Aren't they happy with the number of electrons allotted to them?



No, of course not! Atoms are like people; most of them aren't happy the way they are and would like to be like something else. Just as many people want be like the rich, popular person down the street who throws big parties every night (rather than being like the poor chemistry nerd pecking away at his keyboard), atoms strive to be like the *noble gases,* the elements found in the eighth (and last) column of the Periodic Table. These noble gases (such as helium [He], neon [Ne], xenon [Xe], and argon [Ar]) are the Sean Connerys and Marilyn Monroes of atoms — the atoms that all others wish they were and try to imitate. This desire of atoms to imitate the noble gases provides the driving force for many reactions.

So why do atoms want to imitate the noble gases? What makes these particular atoms so attractive? The answer is their electronic structure. The noble gases are the only atoms that have their outermost shells filled with electrons, while all other atoms have shells that are only partially filled. And

because a filled shell of electrons is the most stable possible electron configuration, it's always in style to have a full shell.

Among the atoms you encounter in organic chemistry, each shell in an atom can hold up to eight electrons, except for the first shell, which can hold two. (The third shell can actually hold 18 electrons, but for somewhat complicated reasons behaves as if it were full when it has eight.) The desire of atoms to have filled electron shells is often called the *octet rule,* referring to the desire of atoms in the second row of the Periodic Table to fill their outer shells with eight electrons, or to imitate those noble gases.



This desire of atoms to imitate the noble gases by filling up their shells is a major driving force of chemical reactions. In fact, the noble gases are so happy by themselves that they are almost completely unreactive. (They are so unreactive that they were called the "inert gases" until some smart-aleck chemists managed to get them to react under unusual conditions.)

The electrons in the outermost shell of an atom are referred to as the *valence electrons.* For bonding, the valence electrons are the most important, and so you most often ignore the *core electrons,* the ones in the inner shells, because they don't participate in bonding. Instead, you focus entirely on the electrons in the valence shell.

To Share or Not to Share: Ionic and Covalent Bonding

Understanding the different kinds of bonding in molecules is important because the nature of the different bonds in a molecule often determines how the molecule will react. The two big categories of bonding are *ionic* bonding, in which the two electrons in a bond are not shared between the bonding atoms, and *covalent* bonding, in which the two electrons in a bond are shared between the two bonding atoms — and these classifications represent the extremes in bonding.

Mine! They're all mine! Ionic bonding

The following is an example of a reaction driven by this desire of atoms to imitate the noble gases. Sodium (Na) combines with chlorine (Cl) to make sodium chloride (NaCl), or table salt, as shown in Figure 2-6. Sodium is an atom found in the first column in the Periodic Table and has one electron in its outermost

shell (one valence electron). Chlorine is in the second-to-last column of the Periodic Table (the column that contains the group VIIA elements) and has seven electrons in its outer most shell (or seven valence electrons). Often, to have an easier time understanding how a reaction is happening, the number of valence electrons an atom owns is represented by the number of dots around the atom. So, you give one dot to sodium because it has one valence electron, and seven dots to chlorine because it has seven.



Figure 2-6: Making NaCl.

To fill its valence octet, sodium could either gain seven electrons or lose one. Likewise, to fill its octet, chlorine could either lose seven electrons or gain one. Atoms generally don't like gaining or giving up more than three electrons, so sodium gives up its one valence electron to chlorine to leave sodium with only filled shells of electrons (by giving up its one electron in its outermost shell, it is left with only filled core shells), and chlorine accepts the electron from sodium and uses it to fill its octet. Because sodium has lost its one electron, it becomes a positively charged ion (a cation), and because the chlorine has accepted an extra electron, it becomes a negatively charged ion (an anion).

Sodium is happy to give up its electron, because when it has done so it has imitated the electron configuration of the noble gas neon (Ne), which has a full valence shell. Similarly, chlorine, by gaining an electron, has imitated the valence shell of the noble gas argon (Ar). Having filled shells makes the atoms happy. When the sodium cation and the chlorine anion combine, you have stable sodium chloride (NaCl, or table salt), and (as far as these atoms are concerned), all is the right with the world.

The attraction between the sodium cation and the chloride anion in sodium chloride is called an ionic bond. In an ionic bond, the electrons in the bond are shared like toys between siblings — which is to say not at all. The anionic species (chloride) has snatched the electron away from the cationic species (sodium). Because the electrons in the bond are not shared, the attraction is one of opposite (positive and negative) charges. You've seen this kind of attraction if you've ever watched two magnets scootch together on a table-top. The "bond" between the two magnets is like the ionic bond between sodium and chloride, albeit on a much larger scale.

The name's Bond, Covalent Bond

A different kind of bonding occurs when two hydrogen atoms come together to make hydrogen gas (H_2) as shown in Figure 2-7, although this reaction is driven by the same desire to imitate the noble gases as in the reaction of sodium and chlorine.



Figure 2-7: Making H_2.

A hydrogen atom has one electron, and so needs one electron to fill its shell. (Remember that the first shell can hold only two electrons, and the remaining outer shells can hold eight electrons.) Because both hydrogen atoms need one electron to fill the first shell, instead of one grabbing the electron from the other, they share their electrons equally. This molecular communism is called a covalent bond, a bond in which the electrons are shared between two atoms. Both hydrogen atoms are now happy, because they each have the electronic configuration of the noble gas helium (He).

Electron piggishness and electronegativity



So how do you know whether a bond is going to be ionic or covalent? A good general tool is to look at the difference in electronegativities between the two atoms. The *electronegativity* of an atom is organic-speak for an atom's electron piggishness. An atom with a high electronegativity will hog the electrons from an atom of low electronegativity. If the electronegativity difference is very large, the bond will be ionic because the atom with the larger electronegativity will essentially hog all of the electrons. If the electronegativity difference is smaller, the bond can be thought of as being *polar covalent:* The electrons are shared, but not equally between the two atoms. And if the electronegativity difference is zero (as it is when two of the same atoms are joined together) the bond can be thought of as *purely covalent:* The electrons are shared equally between the two atoms. The general trend for electronegativities is that as you go up and to the right in the Periodic Table, the electronegativity increases. Fluorine (F), therefore, is the biggest electron swine, because it is the most electronegative element (see Figure 2-8).

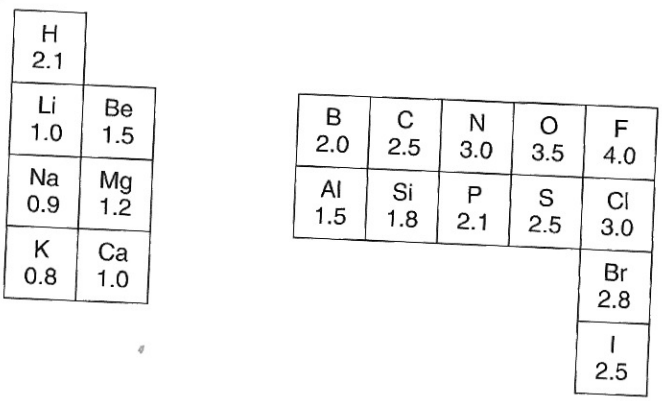


Figure 2-8: The electronegativities of some elements. A larger electronegativity value indicates a bigger electron pig.

Here are the general rules for determining whether a bond will be covalent or ionic.

- If there is no difference in the electronegativities of the two atoms, the bond will be purely covalent.
- If the electronegativity difference between the two atoms is between 0 and 2, the bond will be polar covalent.
- If the electronegativity difference between the two atoms is greater than two, the bond will be ionic.

Table 2-1 shows some examples in which this rule is applied to different bonds.

Table 2-1 Classifying Bonds

Bond	*Electronegativity Difference*	*Classification*
H-H	0	Purely covalent
Cl-Cl	0	Purely covalent
H-Cl	0.9	Polar covalent
C-N	0.5	Polar covalent
Li-F	3.0	Ionic
K-Cl	2.2	Ionic



While ionic bonds are found most often in inorganic compounds (non-carbon-containing compounds), organic compounds are usually held together by covalent bonds. This trend makes sense from looking at the table of electronegativities (see Figure 2-8). Inorganic compounds are often formed when atoms from the left side of the Periodic Table bond with atoms from the right side of the Periodic Table. For example, you often see compounds like LiF, NaCl, KBr, and $MgBr_2$, where atoms from the first or second column bond with atoms found on the far right-hand side of the Periodic Table. Because atoms on the left side of the Periodic Table have a low electronegativity and atoms on the right hand side of the Periodic Table have a high electronegativity, many of these inorganic compounds are ionic, because the differences in their electronegativities are large.

Organic compounds, on the other hand, generally have bonds only between a few different kinds of atoms, and these atoms are generally found between them on the right-hand side of the Periodic Table. Carbon (C), hydrogen (H), oxygen (O), and nitrogen (N) are the most prominent elements you see in organic compounds, but you also see phosphorous (P), sulfur (S), and most of the *halogens* (elements such as fluorine [F], chlorine [Cl], bromine [Br], and iodine [I] that are found in the second-to-last column). Because the electronegativity differences between these atoms are small, bonding between these atoms results in purely covalent or polar covalent bonds, where the electrons in the bond are shared between the two atoms involved in the bond. So, for the most part, organic compounds are held together by covalent bonds.

Separating Charge: Dipole Moments

In a polar covalent bond, the electrons in the bond are not equally shared between the two atoms. Instead, the more electronegative atom bullies most of the bonding electrons away from the less electronegative atom, creating a separation of charge in the bond. This separation is called a *dipole moment.* Dipole moments are often used to explain how molecules react, so learning how to predict the dipole moment of any bond, or of a molecule, is a very important skill to add to your toolbox.

Consider, for example, hydrochloric acid (HCl), shown in Figure 2-9. A quick comparison of the hydrogen and chlorine electronegativities shows that chlorine is the more electronegative atom (refer to Figure 2-6). That means that the electrons in the bond between hydrogen and chlorine are going to be hogged mostly by the chlorine. Because the electrons in the bond are going to be spending most of their time around chlorine and away from hydrogen, this puts a partially negative charge on the chlorine. (The symbol for the lowercase Greek letter delta, δ is used to mean "partial.") Because the electrons

are going to be away from hydrogen, the hydrogen end of the molecule becomes partially positive. Using organic-speak, this separation of charge is called a dipole moment.



Figure 2-9: Seeing bond dipoles.

A strange-looking arrow, called the *dipole vector,* shown in Figure 2-10, is used to show the direction of the dipole moment, or the separation of charge. By convention, the head of the arrow points in the direction of the partial negative charge, while the tail that looks like a + sign points in the direction of the partial positive charge.

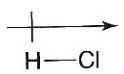


Figure 2-10: Using dipole vectors.

Problem solving: Predicting bond dipole moments

If you want to draw the dipole vector for a bond, you need to look at the electronegativities of the two atoms. The atom with the higher electronegativity becomes partially negative, because this atom is the greater electron hog, and the atom with the lower electronegativity becomes partially positive. You then draw the dipole vector with the head pointing toward the more electronegative atom and the tail pointing toward the partially positive atom. The size of the vector depends on the difference in electronegativity; draw a long vector for large differences in electronegativity, and a short vector for smaller differences.



Being able to predict the direction of the dipole moment is absolutely essential, because the dipole moment can be used to understand how molecules react (see the following section).

Problem solving: Predicting molecule dipole moments

Predicting the dipole moment for a molecule is slightly more complicated than predicting a dipole moment for a bond (see the preceding section). Look at the example of chloroform ($CHCl_3$) in Figure 2-11. To determine the dipole moment of chloroform, the first step you take is to find the dipole vectors of each of the individual bonds. (***Note:*** I've neglected the C-H bond because the electronegativity difference between hydrogen and carbon is so small that its contribution can usually be ignored.) I've drawn each of the vectors for the C-Cl bonds the same size, because each bond is identical.

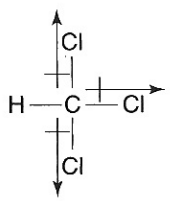


Figure 2-11: The dipole vectors for chloroform ($CHCl_3$).

To determine the dipole moment for the molecule, then, you have to add up each of the individual bond vectors. To do this, you simply line up the vectors from head to tail (it doesn't matter which order you line them up in), as I've done in Figure 2-12. The dipole moment for the molecule points from where you started to where you ended up. In this case, it points to the right.

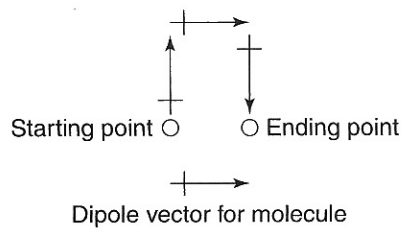


Figure 2-12: Using the dipole vectors to predict the dipole moment for chloroform ($CHCl_3$).



Just because individual bonds have dipole moments does not mean that the molecule has a dipole moment. Consider carbon dioxide (CO_2), shown in Figure 2-13. In this molecule, oxygen is more electronegative than carbon, so you draw the two dipole vectors pointing out. (Double bonds, like the ones between carbon and oxygen in carbon dioxide, are discussed more in Chapter 3.)

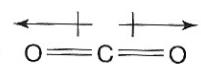


Figure 2-13: Bond dipoles in CO_2.

To predict the dipole for the entire molecule, you have to add up all of the vectors. In the case of carbon dioxide, however, even though there is a dipole for each of the individual bonds, the net dipole moment for the molecule is zero, because the oxygens are pulling in equal and opposite directions, and they cancel each other out, as shown in Figure 2-14. Imagine two equally strong men playing tug-of-war — neither would win, it would simply be a stalemate (unless one of them tripped). Because the net dipole vector is zero, carbon dioxide has no dipole moment.

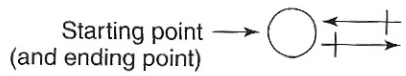


Figure 2-14: CO_2 has no dipole moment.

Seeing Molecular Geometries

VSEPR Theory — VSEPR is pronounced "vesper," and stands for Valence Shell Electron Pair Repulsion — predicts the approximate geometry of bonds around an atom. This theory says that because electrons repel each other, bonds and *lone pairs* (non-bonding electron pairs) around an atom want to get as far away from each other as possible. As far as atoms are concerned, the electrons of other atoms are like clouds of unpleasant atom odor (I suppose this would be abbreviated a.o. rather than b.o.), and so it is imperative for atoms to get as far away from the ungodly a.o. of other atoms as possible.

Extending this theory to molecules, an atom that has two bonds would want the bonds to be 180° apart from each other in a linear geometry, giving the electrons in the bonds the largest separation possible. (See Figure 2-15.) For the same reason, an atom with three bonds would situate the bonds 120° from each other in a *trigonal planar* geometry, and an atom with four bonds would situate the bonds 109.5° away from each other, forming a pyramid-like *tetrahedron*. All of these geometries put the bonds at the maximum distance

apart that is possible. These three geometries (linear, trigonal planar, and tetrahedral) are the main geometries you need to think about in organic chemistry, because the atoms that form organic molecules generally form only four or fewer bonds.

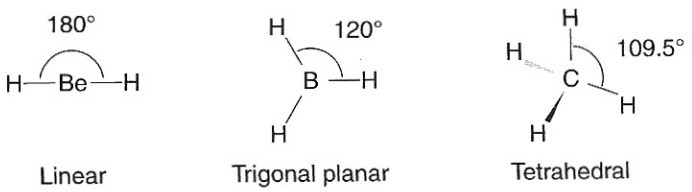


Figure 2-15: The three main geometries of organic molecules.

Mixing things up: Hybrid orbitals

When you know what bond angles molecules are preferred around an atom (see the preceding section), you can see how orbitals' overlapping between atoms leads to bonding. Carbon is a handy model for how bonding works. Carbon has four valence electrons, and so it wants to make four bonds so it can fill its octet and mimic the noble gas neon (Ne). But carbon's electron configuration ($1s^2 2s^2 2p_x^1 2p_y^1 2p_z^0$) shows that the 1*s* and 2*s* orbitals are completely filled, so only the two electrons in the *p* orbitals are available to be shared in a covalent bond. Likewise, carbon wants to have its four bonds oriented in a tetrahedral geometry around the carbon atom, with bond angles of 109.5°. But *p* orbitals are oriented at 90° angles, perpendicular to each other, not at 109.5° angles. So what's a carbon atom to do?

The first thing the carbon atom does is promote an electron from the filled 2*s* orbital into the last empty *p* orbital (see Figure 2-16). This leaves the atom with four orbitals that each contain one electron, perfect for making four covalent bonds. But why would carbon promote the electron? Doesn't putting an electron into a higher energy orbital cost energy? It sure does, but this electron promotion also allows the formation of two additional bonds, which more than pays the cost. It's like investing a dollar and getting back a fiver. Still, carbon has that pesky problem of how to make the orbitals point in the right direction.

So carbon does a most sneaky thing. It mixes the four orbitals together — the three 2*p* orbitals and the 2*s* orbital — and makes four new orbitals, called sp^3 *hybridized orbitals,* each identical, that point at 109.5° bond angles away from each other (how convenient!). These new sp^3 orbitals are called hybridized orbitals because they are hybrids of the original orbitals.

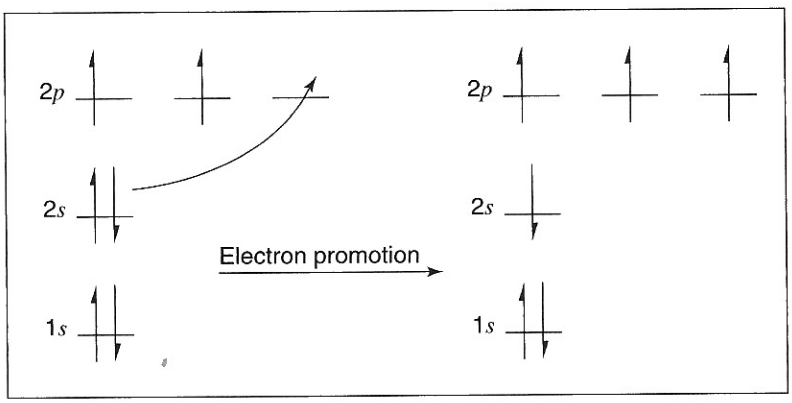


Figure 2-16: Promoting an electron from the 2*s* orbital into the higher-energy 2*p* orbital allows carbon to form four bonds.



In the naming of hybridized orbitals, the superscript indicates the number of orbitals of each type that mix to form the hybrid. But if only one *s* or *p* orbital is involved in the hybridized orbital, then the superscript is omitted. Thus, a hybridized orbital made from one s and three p orbitals is written as sp^3.

The mixed sp^3 orbitals are a weighted average of the orbitals that were tossed into the mixing pot. Mixing three *p* orbitals and one *s* orbital makes the four output sp^3 hybridized orbitals three-quarters *p* in character and one-quarter *s* in character (see Figure 2-17). It's like mixing jars of food coloring. Mix one jar of red food coloring and one jar of yellow food coloring, and you get two jars of orange food coloring, which is the "average" of the two colors.



With orbital mixing, the number of orbitals that are mixed must equal the number of hybridized orbitals that come out at the end. If you mix four atomic orbitals, you must get out four hybridized orbitals. Note that, for clarity, the small lobes of hybrid orbitals are often omitted in drawings.

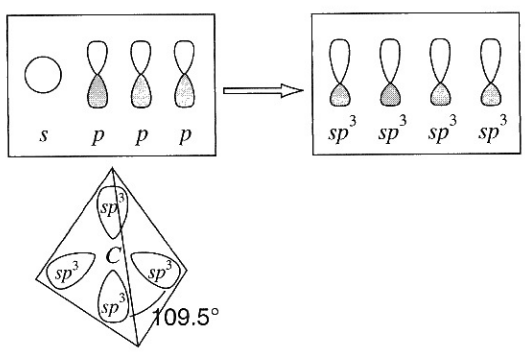


Figure 2-17: Four sp^3 hybridized orbitals are formed when the one *s* and three *p* orbitals are mixed.

What about an atom that has only three bonds to other atoms? In such a case, the four sp^3 hybrid orbitals would be no good because their bond angles are at 109.5°, and you want 120° bond angles for an atom with three bonds so that the bonds can get maximum separation from each other. In that case, the orbitals mix a little differently. Instead of all four orbitals mixing, only three of them mix — the 2*s* orbital, and two of the *p* orbitals — while one of the *p* orbitals remains in its original unhybridized form. See Figure 2-18. Because you're mixing one *s* orbital and two *p* orbitals, the three hybrid orbitals that come out are said to be sp^2 hybridized orbitals, and these bonds are situated at 120° angles to each other.

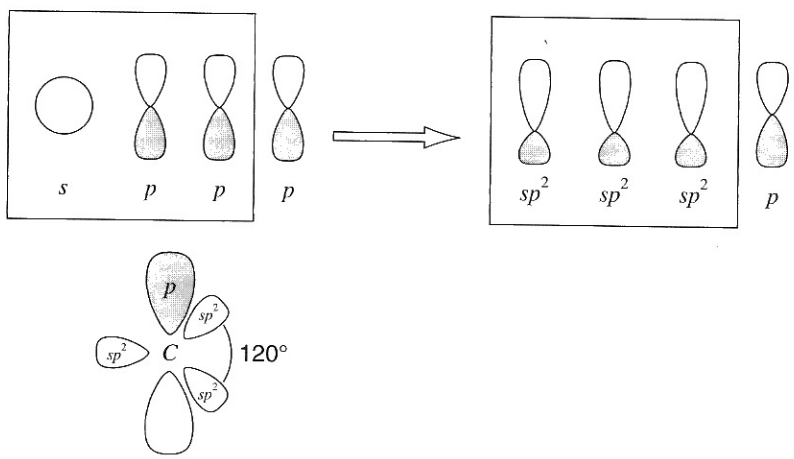
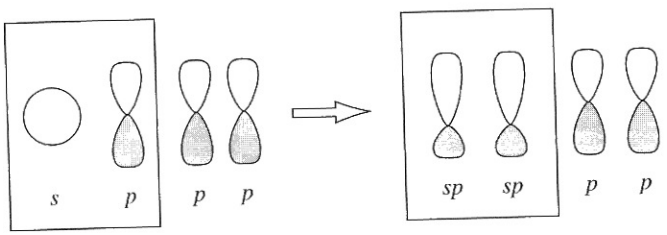


Figure 2-18: Three sp^2 hybridized orbitals are formed when the one *s* and two *p* orbitals are mixed.

For an atom with two bonds, the ideal bond angle is 180°, so only two of the orbitals mix — the *s* orbital and one of the *p* orbitals — and the two remaining *p* orbitals remain unchanged. These two orbitals are called *sp* hybridized orbitals. See Figure 2-19.

Predicting hybridization for atoms

Predicting the hybridization of an atom is often as simple as counting the number of *substituents* (or number of atoms bonded to that particular atom) and lone pairs of electrons around that atom. For BeH_2 (refer to Figure 2-15), the beryllium (Be) has two substituents (two identical H atoms), so it is *sp* hybridized. For BH_3 (also refer to Figure 2-15), the boron (B) has three substituents (three H atoms), so it is sp^2 hybridized. And in methane, CH_4, which has four substituents, the carbon is sp^3 hybridized (refer to Figure 2-15). Knowing the hybridization of an atom can tell you the approximate bond angle and the geometry of the bonds around a given atom. See Table 2-2.



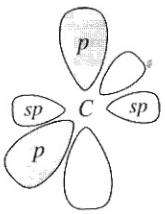


Figure 2-19: Two *sp* hybridized orbitals are formed when one *s* and one *p* orbital are mixed.

Table 2-2 Rule for Determining Hybridization

Number of Substituents (Including Lone Pairs of Electrons)	*Hybridization*	*Approximate Bond Angle*	*Geometry*
2	*sp*	180°	Linear
3	sp^2	120°	Trigonal planar
4	sp^3	109.5°	Tetrahedral

It's All Greek to Me: Sigma and Pi Bonding

Covalent bonds occur when the orbitals of bonding atoms overlap each other. Two kinds of covalent bonds can be formed in organic molecules — sigma (σ) and pi (π).

- *Sigma bonds* are bonds in which orbital overlap occurs between the two bonding nuclei.
- *Pi bonds* are bonds where orbital overlap occurs above and below the nuclei, and not directly between them.

Several different kinds of orbital overlaps can result in sigma bonds. For example, two *s* orbitals could overlap to make a sigma bond (such as in the bond between the two hydrogens in H_2), a hybridized orbital and an *s* orbital could overlap (such as in a C-H bond), or two hybridized orbitals could overlap (such as in a C-C bond). All of these are sigma bonds, because orbital overlap takes place between the two bonding nuclei (see Figure 2-20).

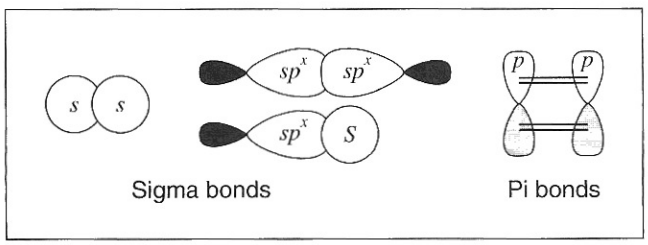


Figure 2-20: Examples of orbital overlap for sigma and pi bonding.

Unlike sigma bonds, only one kind of orbital overlap makes pi bonds (well, only one kind you need to know about in organic chemistry, anyway), and this is the side-by-side overlap between *p* orbitals. With the side-by-side overlap of *p* orbitals, there is no overlap directly between the bonding nuclei, because the *p* orbitals have nodes in this region (a *node* is a region of zero electron density). There is, however, overlap above and below the nuclei. Pi bonds are less common than sigma bonds because they are found only in double and triple bonds, not in single bonds. While *single bonds* are bonds in which two electrons are used to make a bond between atoms, *double bonds* are bonds that contain four electrons; *triple bonds* are made up of six electrons shared between the two bonding atoms.

Now you can apply what you know about sigma and pi bonding and hybridization to draw the orbital diagram of a molecule. Being able to draw the orbital diagram of a molecule is important because this diagram shows you which kinds of orbitals are responsible for the different bonds in a molecule. (This orbital diagram can sometimes be helpful in explaining how certain kinds of molecules react, for example.) Use the three following steps to draw the orbital diagram of a molecule.

1. **Determine the hybridization of each of the atoms.**

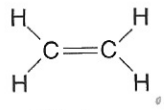
 Note that hydrogen is the only atom whose orbitals remain unhybridized in organic compounds. (Recall that hydrogen contains only the 1*s* orbital in its valence shell.)

2. **Draw all of the valence orbitals for each atom.**

3. **Determine which orbitals will overlap to make the bonds.**

 Double bonds consist of one sigma and one pi bond, and triple bonds consist of one sigma bond and two pi bonds. All single bonds are sigma bonds.

Consider ethylene (C_2H_4) as an example, shown in Figure 2-21.



Ethylene

Figure 2-21: Ethylene.

To determine the orbital picture for ethylene, first you want to determine the hybridization of each of the atoms. Because both carbons have three substituents (that is, they are each attached to three other atoms), both of these atoms are sp^2 hybridized (refer to Table 2-2). This means that each carbon has three sp^2 orbitals plus one p orbital available for bonding. Hydrogen is not hybridized and, thus, has just has the 1s orbital available for bonding. Hydrogen is the only atom that does not hybridize its orbitals for bonding, because it only has one valence orbital, the 1s orbital. Next, you draw each of the atoms with all of its valence orbitals (ignoring all core orbitals, because they are not important in bonding), as shown in Figure 2-22.

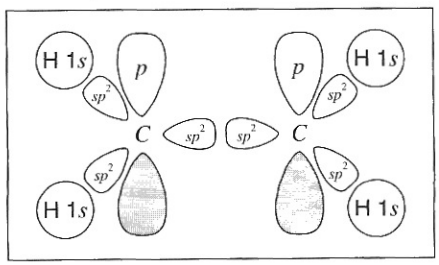


Figure 2-22: The valence orbitals of each of the atoms in ethylene.

Next, you want to determine which orbitals overlap to make the bonds. For each of the C-H bonds, the bond will result from the overlap between an sp^2 orbital on the carbon and the 1s orbital on the hydrogen, making a sigma bond. For the double bond, one of the bonds comes from the two sp^2 hybridized orbitals overlapping between the carbon nuclei to make a sigma bond, while the other bond comes from the two p orbitals overlapping sideways to make a pi bond above and below the carbon nuclei.

This last step generates the orbital representation for ethylene (see Figure 2-23), because the orbitals that overlap to make each bond in the molecule are accounted for. How does knowing which orbitals make up a bond important? Often, the types of bonds in a molecule explain the reactions a molecule undergoes. For example, one of the bonds in ethylene's double bond is a sigma bond and one is a pi bond. Pi bonds are more reactive than sigma bonds (explained in Chapter 9), so one might suspect based on this orbital representation of ethylene that the pi bond is the most reactive bond in this molecule. This observation turns out, in fact, to be the case (as you also see in Chapter 9).

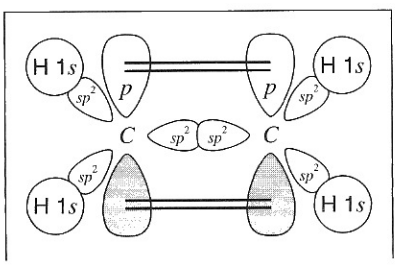


Figure 2-23: The orbital representation of ethylene, showing which orbitals overlap to form the different bonds.

Chapter 3

Speaking with Pictures: Drawing Structures

In This Chapter

- Perfecting your organic-speak
- Drawing Lewis structures
- Seeing structural abbreviations
- Drawing resonance structures

I hope you've had the chance to listen in on a conversation between two chemists in the halls of a cavernous chemistry building as they discussed their experiments. Perhaps you overheard snatches of their conversation: "I don't get it," one might have said, "My proton NMR showed two multiplets one part per million upfield from the aromatic protons"; or maybe you heard, "I made the alkene via the Wittig, but for the life of me I simply could not get the reduced nitro group to react with the t-butyl chloride using an S_N1 in ethanol!" Or perhaps, "We return to planet Beldar with the earthlings in eight lunar cycles of Klathryn!" And you thought, "Now *what* language were they speaking?"

They were speaking organic, of course (mostly), which hasn't been classified yet as a foreign language, but perhaps could be, because learning organic chemistry is a lot like learning a foreign language. Organic chemistry has its own jargon, as the snatches of conversation you overheard show (though after you've read this book and are fluent in organic you'll be able to understand what they were talking about). But I would argue that the similarity goes deeper than that. The words are different, too.

Before you can speak German or Japanese or Swahili — or any foreign language, for that matter — you need to learn what the different words mean. Similarly, before you can "speak organic," you need to learn how to draw structures. Structures are the "words" of the organic chemist, and becoming fluent in drawing structures is absolutely essential if you are to do well in organic chemistry. Drawing structures might seem strange at first, and probably even

intimidating, but with practice you'll soon get the hang of it. Like speaking a foreign language, with enough practice drawing organic structures will simply become second nature (and kind of fun, too).

In this chapter, I give you the vocabulary for speaking organic chemistry by showing you how to draw organic structures using the standard Lewis convention. I also walk you through the ways that organic chemists abbreviate Lewis structures, both for clarity and for when they are feeling lazy (which, admittedly, is most of the time). I also show you how to draw resonance structures, which are used to correct for a flaw in the Lewis structure model.

Models and molecules

People have a hard time comprehending objects that are either huge or tiny. That's because our minds think in terms of the sizes of the things we encounter in our daily lives. A kilometer is about as far as our walk across campus; two centimeters is about the length of our pinky tips. To us, these sizes make sense; we can relate to them. But comprehending gargantuan lengths, like the distance between the earth and a distant star millions of light years away, or itty-bitty lengths, like the distance across an atom (a distance of only a few hundred picometers), is mind-boggling.

This difficulty creates a problem for chemists. How can they understand atoms and molecules if they are so small that it boggles their minds just to think about them? How can they describe, organize, and classify things that they cannot see? In short, how can they be scientific about the study of chemistry?

In addition to our inability to comprehend such small things is the added complexity that atoms don't behave in the same way as objects of a larger scale; they don't behave like the things we see in our everyday lives — things that we can see or touch or throw, things like stink bombs or chemistry texts. Molecules behave in very bizarre ways as a result of their smallness, and human intuition based on the big world of everyday objects is no help in understanding the tiny world of molecules. For atoms, the classical physics that you've been taught since grade school fails, and fails miserably. This is because something that is very, very small (like an electron) has been found to behave both like a particle (which you might expect) and as a wave (which you wouldn't). Electrons are small enough that they have the ability to "tunnel" through a barrier (the equivalent of a person walking through a wall), and they can exist in two places simultaneously, in addition to other very bizarre behaviors.

So chemists must use models to describe molecules and their weird behavior. Chemists use models to describe the way a molecule is put together — where the electrons are and which atoms are attached together and in what way — and to represent how reactions might occur. The primary model used in organic chemistry is the Lewis structure. Although Lewis structures are only approximate models of how molecules look in actuality, they really do an excellent job of showing the connectivity of atoms. These models, however, are not always perfect for describing the exact locations of certain electrons, as I discuss in the section about resonance structures later in the chapter.

Picture-Talk: Lewis Structures

A Lewis structure is the chemist's way of depicting an infinitesimally small molecule on a macroscopic piece of paper. A Lewis structure shows what atoms are connected to each other, and it shows where the electrons in the molecule reside. Single bonds between two atoms are represented with a single line (—), signifying two shared electrons; double bonds are represented with a double line (═), signifying four shared electrons; and triple bonds are represented with a triple line (≡), signifying six shared electrons (refer to Chapter 2 for more on bonding). Nonbonding electrons are indicated with dots on the atoms on which they reside.

Electrons, electrons, electrons: These little guys are the keys to chemistry. They are what organic chemists care most dearly about. The neutrons and protons stay fixed in their little round shack at the nucleus, but the electrons are adventurous, bustling about making new bonds and breaking old ones, and so organic chemists concern themselves mostly with what happens to the electrons. Because electrons form and break bonds (and protons and neutrons do not), the focus throughout organic chemistry is on where the electrons are and where they are going in a chemical reaction. So, for the most part, you ignore the protons and neutrons in the nucleus, because these remain constant.

Taking charge: Assigning formal charges

The first thing you want to be able to identify on a Lewis structure is which atoms have formal charges. Electrons are negatively charged, so an atom that is missing one or more electrons will have a positive charge. An atom that has one too many electrons will have a negative charge. Being able to quickly determine the charge on any atom in a given molecule is extremely important. So here's a quick-and-dirty equation for determining the formal charge on an atom:

formal charge on an atom = valence electrons – dots – sticks

Here "dots" is simply the number of lone-pair electrons around the atom, while "sticks" is the number of bonds off of the atom. (A single bond is one stick; a double is two; a triple, three.) The best way to see this is to try one. So apply this equation to NH_2, shown in Figure 3-1, to calculate the formal charge on the nitrogen atom.

Figure 3-1: The amide ion. 

Just plug the values into the formula. Nitrogen is in the fifth column of the Periodic Table and so has five valence electrons; it has four dots (four nonbonding electrons), and two sticks (two bonds).

formal charge = 5 valence electrons – 4 dots – 2 sticks = –1

The formal charge on the nitrogen, then, is –1, so in this molecule nitrogen is anionic. Using this same approach, you should be able to apply this formula quickly to all the atoms in a molecule. Still, even though this equation is fairly simple to use, applying it to every atom in a molecule is tedious. You want to be able to simply look at a structure and within a couple of seconds determine which atoms have charges.

Fortunately, with enough practice, you'll quickly recognize certain patterns for different atoms that will indicate whether the atoms are neutral, positively charged, or negatively charged. For example, if carbon has four bonds, it will be neutral, if it has three bonds, it will be positively charged, and if it has three bonds and a lone pair, then it will be negatively charged. You can see this generality to be true for yourself by plugging these different configurations for carbon into the equation for formal charge just shown.



Knowing that a neutral carbon atom always has four bonds lets you scan a molecule quickly to identify carbons that don't have four bonds, and, when you find one, say to yourself, "Aha! This carbon must have a charge." For nitrogen, you look to see which nitrogen atoms don't have three bonds and a lone pair; for oxygen you look to see which ones don't have two bonds and two lone pairs, and so forth. This way, you won't need to apply the formula to every atom (although you can if you want to); you just look to see which atoms differ from the typical number of bonds found around an atom in its neutral form. I show these patterns for the most common elements in organic compounds in Figure 3-2.

Chemists, in fact, use specific jargon to describe typical bonding patterns of atoms. The number of bonds around a neutral atom is referred to as that atom's *valency*. Carbon is tetravalent ("tetra" means four), because carbon has four bonds to other atoms when it's neutral; nitrogen is trivalent, because it has three bonds to other atoms (plus a lone pair) when it's neutral; oxygen is divalent, because it has two bonds to other atoms (plus two lone pairs) in its neutral form; and halogens (elements such as fluorine [F], chlorine [Cl], bromine [Br], and iodine [I]) are monovalent, because they have one bond to another atom (plus three lone pairs) when they are neutral.

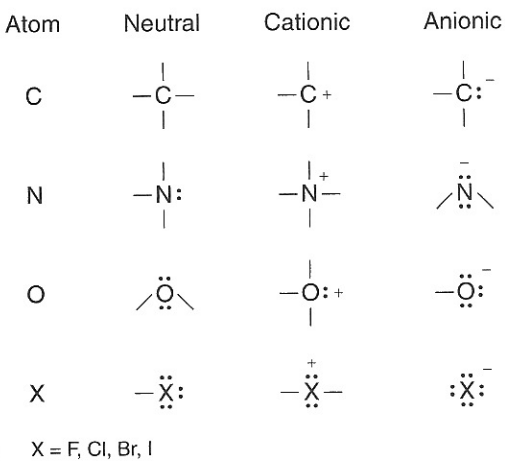


Figure 3-2: Some common charges on atoms.

Drawing structures

In addition to calculating charges, you also need to be able to quickly draw organic structures and interpret what the drawings mean, because these are the words you will use to speak organic chemistry.

Organic chemists draw structures in several different ways, and because the different styles have different uses, you should be familiar with all of them. The most complete way of drawing organic structures is with the full Lewis structure (sometimes called a Kekulé structure; for more on Kekulé see Chapter 20). A Lewis structure explicitly draws out all of the bonds in a molecule (an example is given in Figure 3-3). The lone pairs on atoms may or may not be shown in a Lewis structure (they often aren't), but formal charges are always shown. Later in the chapter, I show you how to determine the number of lone pairs on a given atom when these lone pairs aren't explicitly shown (don't worry, it's not difficult).

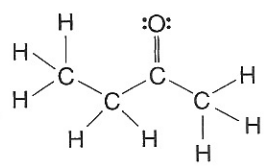


Figure 3-3: The full Lewis structure for butanone.

Full Lewis structures most faithfully show the structure of a molecule and how the molecule is put together, because every bond and every atom is shown. But this method of structure drawing can become tedious and overwhelming

when you draw larger molecules. To make structure drawing quicker and the interpretation of change in a molecule easier to spot, chemists use shorthand notation, just as you might use special abbreviations when you Instant Message your friends on the Internet.

Atom packing: Condensed structures

One such structure abbreviation of the full Lewis structure is called a condensed structure. In a condensed structure, the bonds between carbon and hydrogens are not explicitly shown; instead, each carbon and the attached hydrogens are grouped together into a cluster (such as CH_2 or CH_3), and these clusters are written in a chain that shows the connectivity between the carbons. The carbon-carbon bonds may be explicitly shown, or they may simply be assumed. Condensed structures with shown and unshown bonds between the clusters are given in Figure 3-4 for the molecule butanone.

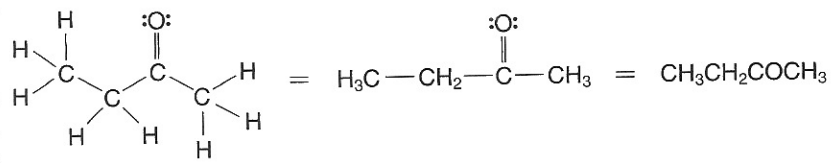


Figure 3-4: Condensed structures of butanone.

Condensed structures are most useful when the molecule consists of a straight chain of atoms; elaborate structures that contain rings are difficult to portray with condensed structures. When two or more identical groups are attached to an atom, parentheses with a subscript can be used to abbreviate the structure even further. In this case, the subscript indicates the number of identical groups that are attached to the atom. An example of this grouping for condensed structures is given in Figure 3-5 for diethyl ether.

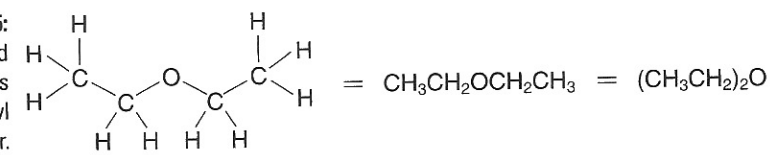


Figure 3-5: Condensed structures for diethyl ether.

Parentheses are also used when a chain becomes very long and a unit is repeated many times (for instance, when a CH_2 unit is repeated). Here, the

subscript after the parentheses indicates how many times the unit is repeated, as shown for heptane in Figure 3-6.

Figure 3-6: Heptane condensed structure.

$$CH_3CH_2CH_2CH_2CH_2CH_2CH_3 = CH_3(CH_2)_5CH_3$$

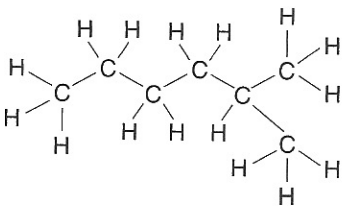
Structural shorthand: Line-bond structures

The most common method of structure drawing, however, is called the line-bond structure. In these structures, each point (or *node*) on a jagged line is assumed to be a carbon atom. Hydrogens attached to carbons are not explicitly shown in a line-bond structure. But because each carbon is presumed to be neutral unless a charge is explicitly written on the structure, this method of drawing structures assumes that you can mentally supply the number of hydrogens attached to each carbon by making the total number of bonds equal to four. So, if a neutral carbon is shown having two bonds to other carbon atoms, then it must also be bonded to two additional hydrogens that are not shown. Figure 3-7 shows the line-bond structure for isoheptane.



The general rules for line-bond structures are as follows:

- Each point on a jagged line is assumed to be a carbon atom.
- The ends (tips) of lines are assumed to be carbon atoms.
- All hydrogens attached to non-carbon elements (like N, O, S, and so on) must be explicitly shown.
- All atoms are presumed to be neutral unless a charge is specifically shown.



Full Lewis structure

$CH_3(CH_2)_3CH(CH_3)_2$

Condensed structure



Line-bond structure

Figure 3-7: Structures for isoheptane.

Converting Lewis structures to line-bond structures

As shown in Figure 3-8, to convert a full Lewis structure to a line-bond structure, a jagged line is used to represent straight chain molecules, with each point (including the ends of the structure) representing a carbon atom.

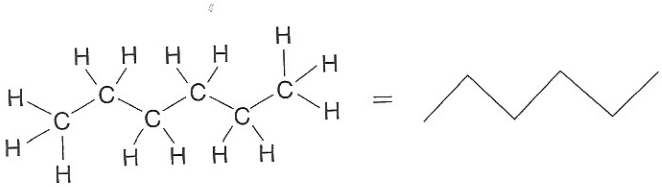


Figure 3-8: Line-bond structure for hexane.

In line-bond structures, rings are represented by polygons, with each point representing a carbon atom, as shown for the five-membered ring in Figure 3-9. A triangle is a three-carbon ring (which, of course, is the smallest possible ring size); a square is a four-carbon ring; a pentagon is a five-carbon ring; and so forth.

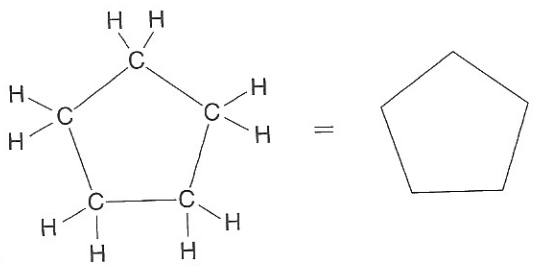


Figure 3-9: Cyclopentane line-bond structure.

Multiple bonds are explicitly drawn out. Triple bonds are drawn in a straight line as shown in Figure 3-10, and are not jagged like single bonds (I talk about why in Chapter 9).

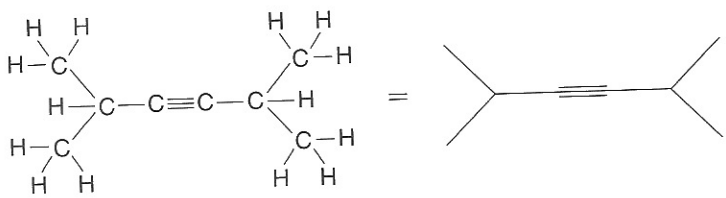


Figure 3-10: Diisopropyl acetylene.

Hydrogens attached to any atom other than carbon (atoms such as oxygen [O], sulfur [S], and nitrogen [N]) must be explicitly shown; only hydrogens attached to carbons are not shown. Figure 3-11 shows an example of how to draw non-carbon atoms in line-bond structures.

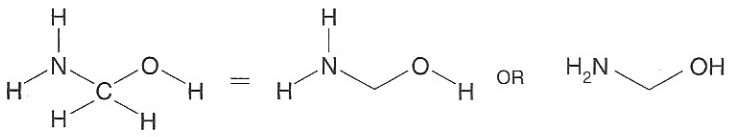


Figure 3-11: Amino methanol.

This line-bond method of structural representation is probably the method most commonly used by organic chemists — it's easy to draw, it's convenient, and it's uncluttered in comparison to the full Lewis structure. My guess is that you will prefer at least initially to use full Lewis structures to represent molecules rather than this line-bond method, because Lewis structures don't require you to mentally supply the missing hydrogens.

At first, using full Lewis structures in your drawings is probably an excellent idea, because this structure has no structural abbreviations (just as you would want to learn how to speak with proper English before learning language abbreviations with Instant Messaging). But you should familiarize yourself with line-bond drawings right away so you can quickly become comfortable using them. Your organic chemistry textbook — and your teacher — will likely use line-bond structures almost exclusively later in the course, so it will be to your advantage to know how to draw and interpret line-bond structures.

Determining the number of hydrogens on line-bond structures

Being able to quickly "see" how many hydrogens are on each carbon in a line-bond structure takes practice. But the math, at least, is simple. A neutral carbon has four bonds. So if a line-bond structure shows a carbon that has three bonds to other atoms, it must have one implicit hydrogen; if it shows a carbon that has two bonds, then it must have two implicit hydrogens; if it shows a carbon that has only one bond, then it must have three implicit hydrogens. In Figure 3-12, I show a line-bond structure and point out the number of hydrogens assumed to be attached to each of the carbons.

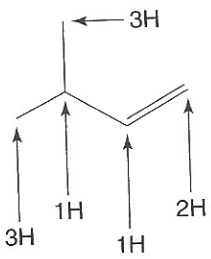


Figure 3-12: Counting the assumed hydrogens.

Getting the hang of drawing line-bond structures takes a bit of work, but once you do, the payoff will be big, because you'll be able to draw structures much faster (which is a significant issue when you're dealing with a large number of structures), and you'll be able to see chemical changes much more easily than if you were using the full Lewis structures (important when you begin chemical reactions of organic molecules). You'll also better understand the textbook and your instructor when they use these line-bond structures.

Quite often, you see structures drawn that combine these three different methods of structure drawing. In other words, it's not a requirement that an entire molecule be drawn using only one of the drawing methods. It's not unusual to see parts of a molecule drawn out with the full Lewis representation, parts drawn in condensed structure form, and parts drawn using the line-bond format. Chemists often have good reasons for doing this — to emphasize certain important parts of a molecule, for example — but at the beginning, when you're just trying to get everything straight in your head, you can easily get confused if a structure is drawn that combines the different structure drawing styles. Figure 3-13 shows an organic molecule that was drawn using a combination of structure drawing methods.

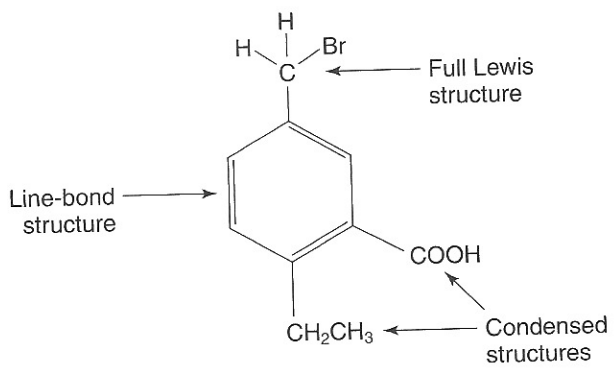


Figure 3-13: A structure drawing that combines the three different styles.

So lonely: Determining lone pairs on atoms

Most often, lone pairs on atoms are not shown explicitly because chemists assume that you can determine for yourself the number of lone pairs on the atom. One way to determine the number of lone pairs (if they are not shown) is to simply plug the information into the rearranged equation for the formal charge, where "Dots" is simply the number of nonbonding electrons.

dots = valence electrons – sticks – formal charge

The best way to master this is by practicing, so go ahead and try one. To determine the number of lone pairs on the nitrogen atom in NH_2^-, you plug into the equation the number of valence electrons for nitrogen (five), the number of sticks (two, because nitrogen has two bonds, one with each of the two hydrogens), and the formal charge on the atom (–1 in this case).

Dots = 5 – 2 – (–1) = 4

So NH_2^- has four nonbonding electrons, or two lone pairs of electrons (because there are two "dots" in every lone pair).

As is the case with distinguishing formal charges, after a while you'll become practiced enough at figuring out the number of lone pairs that you won't need to do this calculation, because you'll recognize the patterns of electrons and bonds. At that point, you'll know that a negatively charged nitrogen will have two lone pairs, that a negatively charged carbon will have one lone pair, that a neutral oxygen will have two lone pairs, and so on (refer to Figure 3-2 for the other patterns). But it's going to take some work before it becomes second nature, so practice, practice, practice!

Problem Solving: Arrow Pushing

Now for the squishy part. If structures are the words of organic chemistry, then arrow pushing is the grammar and syntax of organic chemistry. And I know how much everyone loves grammar. Figure 3-14 shows the different kinds of arrows used in organic chemistry. Knowing what the arrows represent and how to use them properly will help you understand organic chemistry. (Like English professors, chemistry professors are very picky about using this "grammar" correctly.)

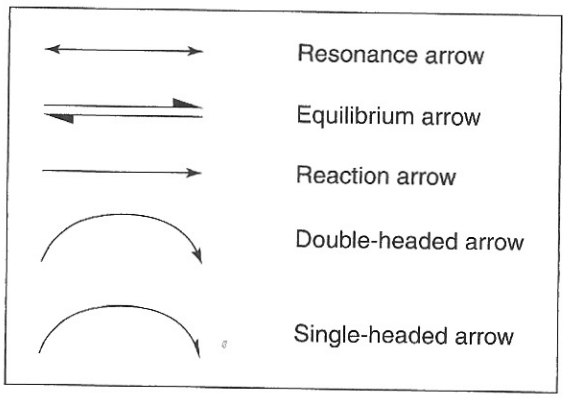


Figure 3-14: The types of arrows used in organic chemistry.

In organic chemistry, you see five major types of arrows:

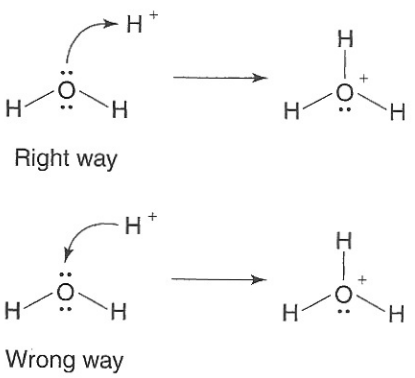
- **Resonance arrow:** Used to indicate movement between resonance structures (which I talk about in the next section).
- **Equilibrium arrow:** Used to show reactions governed by equilibria (see Chapter 12). Making one of the equilibrium arrows longer shows the direction of the equilibrium in a reaction (in other words, which side of the reaction — reactants or products — is favored).
- **Reaction arrow:** Used to show the change of molecules by a reaction.
- **Double-headed arrow:** Used to show the movement of two electrons.
- **Single-headed arrow:** Used to show the movement of one electron.

Organic chemists use single- and double-headed arrows to show the movement of electrons (sometimes these are called *fishhook arrows* because they look like fishhooks). Double-headed arrows are much more common than single-headed arrows, simply because most reactions involve the movement of lone pairs and bonds — each of which contains two electrons. Single-headed arrows are used for describing free radical reactions (described in Chapter 7), because these reactions involve the movement of single electrons. You need to become as good as Robin Hood at using these arrows.

Mastery of so-called "arrow-pushing" is essential to mastering organic chemistry — and, importantly, to doing well in the class! Arrow pushing is something that can't be learned in one sitting. This kind of grammar takes lots and lots of practice to master. (I hope this theme is starting to become repetitive.) Arrow pushing is organic-speak for showing *how* a chemical change takes place. To do this, organic chemists use these single- and double-headed arrows, which show how you get from one structure to the next in a reaction

(or in a resonance structure, which is described in the next section) by showing the movement of electrons. Double-headed arrows, by convention, are used to show the movement of electrons. Therefore, you always *draw arrows from electrons toward where they are going*, never the other way around. I think most students would prefer to have arrows show the movement of atoms rather than show the movement of electrons. But using an arrow to show the movement of atoms is wrong, and if you make your arrows do that on an exam, it will almost certainly cost you points. If, for example, you want to show water being protonated (receiving an H^+ ion) by acid, you would show one of the lone pairs on water's oxygen attacking the proton (the H^+), not the proton moving onto the water.

Because H^+ has no electrons (hydrogen has lost its one electron to become a positively charged cation), one might ask when would it be correct to show an arrow coming from an H^+. As King Lear may have said had he been an organic chemist: "Never, never! never! never! never!" Figure 3-15 shows the correct and incorrect ways to show the movement of electrons using a double-headed arrow.



Right way

Wrong way

Figure 3-15: The right and wrong ways to use double-headed arrows to show electron movement.

Drawing Resonance Structures

Lewis structures show the locations of electrons correctly most of the time — but not always. To correct for a flaw in showing the locations of certain electrons in Lewis structures, chemists use *resonance structures*. Organic chemists use these resonance structures — ceaselessly, from the beginning of the course straight to the end — to account for a flaw in showing the locations of certain lone-pair and pi electrons in Lewis structures (pi electrons are electrons found in pi bonds; refer to Chapter 2). You can't get through organic chemistry without being able to draw the dreaded resonance structures and without understanding what these structures mean.

The Lewis structure for a carboxylate anion (RCO_2^-, where R stands for *rest of molecule*) provides a good example of how Lewis structures are not always the best way to describe certain molecules. This Lewis structure (see Figure 3-16) predicts one double bond between carbon and one of the oxygens, and one single bond between carbon and the oxygen that contains the negative charge. According to this Lewis structure, the two different C-O bonds are different. Instead, the actual structure is one in which both of the carbon-oxygen bonds are identical — with each C-O bond having some single-bond qualities and some double-bond qualities — and each of the oxygens shares the negative charge equally.

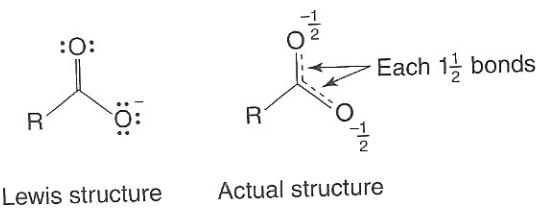


Figure 3-16: The Lewis structure of a carboxylate ion compared to the actual structure.

Because this Lewis structure fails to correctly account for the location of the electrons, organic chemists use resonance structures to correct for this flaw. In general, any time more than one valid Lewis structure can be drawn for a given molecule, each of these alternate structures is considered a resonance structure, and the actual structure of a molecule will look like a hybrid of all of the different resonance structures.

Rules for resonance structures

Here are the three basic rules for resonance structures:

- **Atoms are fixed and cannot move.** Because the purpose of resonance structures is simply to account for alternative locations of electrons, all atoms stay in fixed positions. Only the distribution of the electrons in the molecule changes from one resonance structure to the next.
- **Only lone-pair electrons and pi electrons — which are only found in double and triple bonds — can move.** Single bonds stay put (to review pi bonds, refer to Chapter 2).

- **You can't break the octet rule.** This old law still applies. To put this rule into practical terms, the sum of an atom's lone pairs and bonds cannot be greater than four.

For example, the carboxylate anion in Figure 3-17 can be represented by two different and equally valid Lewis structures, one in which the negative charge rests on the top oxygen, and one in which the charge rests on the bottom oxygen. So which Lewis structure represents the actual molecule? The answer: Neither one does! In fact, no single resonance structure describes a molecule perfectly, but the correct structure lies somewhere in between; the correct structure is a hybrid of all of the resonance structures. In the case of the carboxylate anion, each of the C-O bonds is neither a double bond or a single bond, but a bond that is somewhere in between (one-and-a-half bonds).



You might ask why chemists don't simply draw the hybrid drawing (like the one shown in the right-hand portion of Figure 3-17), with the dotted line representing the partial (one-and-a-half) bonding character. One reason is that this drawing doesn't show the *number* of electrons in the molecule, so this drawing is an inconvenient representation for showing the reactions of that molecule. Instead, multiple resonance structures are used to represent the hybrid nature of the actual structure.

Note the use of the double-headed resonance arrow (⟷) in Figure 3-17 to show the two equivalent resonance structures. This arrow serves as a reminder that resonance is not a reaction, not an equilibrium process, and not a change of any kind in a molecule. Instead, these resonance structures are simply a way of accounting for the proper electron distribution of a *single molecule* on a piece of paper. A molecule does not flip between different resonance structures, back and forth, back and forth. It exists instead as one structure all of the time, one that simply looks like the hybrid of all of the possible resonance structures.

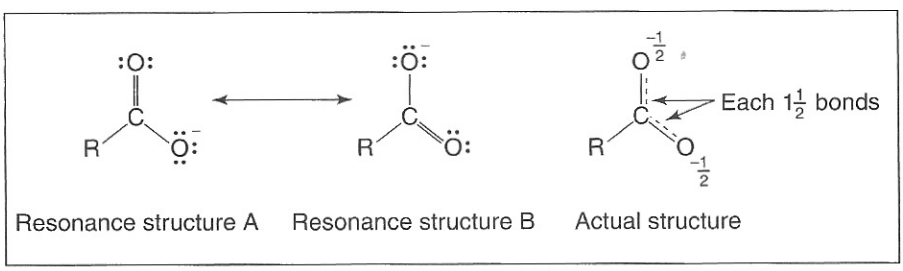


Figure 3-17: Double-headed resonance arrows are used to convert between resonance forms.

For the carboxylate anion, there are two valid Lewis structures that can be drawn, and so each of these are considered resonance structures.

Problem solving: Drawing resonance structures

So how do you recognize when a structure has alternative resonance structures, and how do you go about drawing resonance structures for a given molecule? Any time a molecule can be represented by an alternative valid Lewis structure, then all such alternatives are considered resonance structures. But how do you determine when a molecule can be represented by alternative Lewis structures?

One way that resonance structures are found is by pushing the nonbonding and pi electrons around with arrows. (Recall that pi electrons are electrons that contribute to double and triple bonds. Read more in Chapter 2.) Electron-pushing arrows are used to convert one resonance structure into the next. It's a bit unfortunate that usually the first "arrow-pushing" you do in your organic chemistry course is for resonance structures, because the meaning behind the arrow-pushing used for resonance structures is entirely different than the meaning behind the arrow-pushing that you use again and again later in the course to show how a reaction occurs. They are fundamentally different, even if they seem similar.

How so? In the preceding section, I use a double-headed arrow in Figure 3-17 to show the protonation of water (the addition of H^+ to water). In that figure, the arrow is used to show how the reaction happens: The lone-pair electrons on the oxygen attack the proton (H^+), forming a new bond.

Resonance structures use arrows for a different purpose. They don't show how a reaction happens. Instead, the arrows are simply used as a convenient tool to determine all of the alternative resonance structures. These arrows are not really showing the movement of electrons, because resonance structures are simply our way of modeling a single, unchanging molecule.

With that in mind, a few common patterns can be used to recognize when a structure can be better described using resonance structures. In the sections that follow, I take you through four kinds of structural features that are indicative of molecules that will have two or more resonance structures. In addition to these four patterns, keep in mind that resonance structures must adhere to the three basic rules listed above: Atoms are fixed and don't move, you must leave single bonds fixed, and you can't break the octet rule. Now, look at each of these patterns individually.

A lone pair next to a double bond or triple bond

You use arrows to convert one resonance structure into the other. Note that in cases where a lone pair is adjacent to a double bond, at least two arrows are drawn. The first begins at the lone-pair electrons and moves these electrons in the direction of the double bond. The next arrow places the double bond electrons onto the adjacent carbon as a lone pair.



You can't stop after you've drawn just the first arrow because to do so would result in a structure that would violate the octet rule. To prove this to yourself, draw out all of the hydrogens in the structure and then push some arrows!



Figure 3-18: Lone-pair resonance.



A common confusion among students involves the frequent symmetry of resonance structures. They see that both of the resonance structures look like the same thing — in other words, if you were to flip one of them over like a pancake, one would be superimposable on the other. So aren't they the same? The answer is no, because the first rule of resonance structures is that the atoms cannot move, so you could not perform such a flip without moving the atoms. Therefore, even though the resonance structures "look the same," each of them is a *different* resonance structure and must be included.

A cation next to a double bond, triple bond, or lone-pair of electrons

In a somewhat similar situation, a double bond that is situated next to a positive charge will also yield resonance structures. In this case, you cannot draw the arrow from the positive charge because there are no lone-pair or pi electrons on that carbon. (Recall that with arrow-pushing you never draw an arrow originating from a positive charge because arrows always originate from electrons.) Instead, you move the double-bond electrons onto the adjacent single bond, making a new double bond. This re-forms the double bond on the other side of the molecule and shifts the positive charge from the left side to the right, as shown in Figure 3-19. (Insert the hydrogens and calculate the charges for yourself if you don't believe me!) Note that the octet rule is not violated here.



Figure 3-19: Pi bond resonance.

Similarly, when a lone pair of electrons is situated next to a positive charge, an alternative resonance structure involves moving the lone pair of electrons in the direction of the cation to form a double bond. The positive charge then moves to the atom that originally held the lone pair, because that atom has become deficient in electrons. See Figure 3-20.

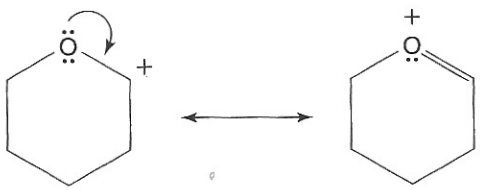


Figure 3-20: Lone pair resonance.

A double or triple bond containing an electronegative atom

When a double or triple bond includes an electronegative atom (like oxygen or nitrogen), an alternative resonance structure can be found by moving one of the double (or triple) bonds onto the electronegative element as a lone pair. In such situations, the electrons always go onto the more electronegative element, not the carbon. (Find out more about this rule in the "Assigning importance to resonance structures" section later in this chapter.) An example of this kind of resonance is shown in Figure 3-21 for acetone (the chemical in fingernail polish remover).



Figure 3-21: Pi bond resonance.

Alternating double bonds around a ring

When double bonds alternate all the way around a ring, you can move each of the double bonds over to the next carbon to make an alternative resonance form. Benzene, for example, has two resonance structures, as shown in Figure 3-22. Here you would break the octet rule if you were to stop after drawing either one or two of the arrows. So, you have to go all the way around the ring.

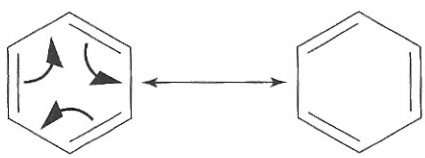


Figure 3-22: Benzene resonance structures.

Drawing more than two resonance structures

Sometimes a structure will have more than two resonance structures. Figure 3-23, for example, shows a molecule that has four resonance structures. If you were asked to draw all of the resonance structures for this molecule, you would start by recognizing that the molecule had a double bond containing an electronegative atom (the C=O unit), which conforms to pattern number three described in the preceding section.

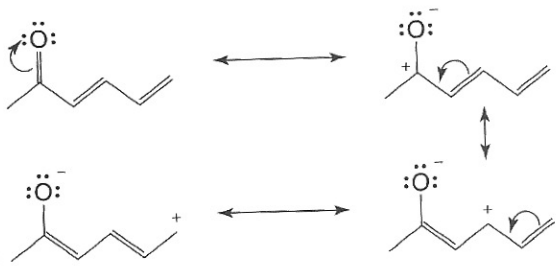


Figure 3-23: Four resonance structures for 2-hexadienone.

Drawing the resonance structure by moving the double-bond electrons onto the oxygen creates a species with a positive charge on carbon. But this is not the end of the resonance structures. This positive charge, now, is next to a double bond, which is another of the common patterns (pattern number two) discussed in the previous section. So, another resonance structure can be drawn by moving the double-bond electrons onto the single bond to the left, which moves the location of the positive charge. But there is still one more resonance structure that can be drawn. Moving the last double bond over to the left in the same fashion as you did previously puts the positive charge on the end carbon atom. All four of these structures are valid resonance structures.

Often, you can get to any of the resonance structures in a single step. Figure 3-24 illustrates this one-step process. Generally, though, drawing out all of the resonance structures one at a time like I've shown (at least until you get the hang of it) is helpful to make sure that you don't leave out any resonance structures.



Figure 3-24: Converting between resonance structures in one step.

Assigning importance to resonance structures

Some resonance structures will contribute more to the overall hybrid than others. As a rule, the more stable resonance structures will contribute more to the hybrid than unstable ones. Three major factors are used to determine the relative stability of resonance structures (and therefore their relative importance). In this section, I illustrate each of these three factors.

Fewest charges

The resonance structures that have the fewest charges within the molecule will contribute the most to the overall hybrid. This rule makes sense because keeping positive and negative charges separate from each other costs energy, just as it would cost energy to pull two magnets apart. For the molecule acetone, shown in Figure 3-25, the first resonance structure is uncharged, so it will contribute more to the overall hybrid than the resonance structure on the right that has both positive and negative charges.

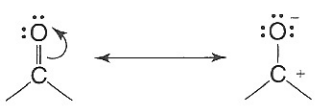


Figure 3-25: Acetone resonance structure.

Charges on the best atoms

Negative charges generally prefer to rest on electronegative elements (elements such as oxygen and nitrogen), while positive charges will prefer to rest on electropositive elements (such as carbon). An alternative resonance structure for acetone is one in which the negative charge rests on the carbon and the positive charge rests on the oxygen. This resonance structure is considered a bad resonance structure (see Figure 3-26). Because oxygen is an electronegative atom (an electron pig), it really does not want to have a positive charge; therefore, the resonance structure on the right would contribute an insignificant amount to the overall hybrid. Although technically it would be considered a valid resonance structure, this resonance form is never drawn because it is so unstable that it would not significantly contribute to the overall hybrid.

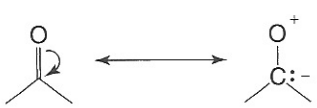


Figure 3-26: Bad resonance structure.

In the example shown in Figure 3-27 both resonance structures *would* contribute to the overall hybrid. In this example, the negative charge rests on either oxygen (in the right-hand structure) or carbon (in the left-hand structure). Because oxygen is more electronegative, the oxygen is more comfortable holding the negative charge than is carbon, so the resonance structure on the right would contribute more to the overall hybrid.



Figure 3-27: Comparing charge stability.

Filled octets

In the next example, shown in Figure 3-28, you may expect, based on the last argument about placing positive charges on electropositive atoms and negative charges on electronegative atoms, that the resonance structure on the left would contribute more to the overall hybrid, because carbon would be more willing to hold a positive charge than would nitrogen. However, this analysis neglects one key factor: A full octet of electrons.

In fact, the resonance structure on the right contributes the most to the overall hybrid, because every atom in that resonance form has a full octet of electrons. In the resonance structure on the left, the carbon does not have a complete octet, owning only six electrons in its outermost shell. Generally, the desire of atoms to achieve a full octet trumps the desire to put the charges on the best atoms. This is why the resonance structure on the right contributes more to the overall hybrid than does the resonance structure on the left, even though the structure on the right has the charge on a less preferable atom.



Figure 3-28: Octet considerations trumps charge considerations.

Common mistakes in drawing resonance structures



Here are four common mistakes that students make in drawing resonance structures. Avoid these at all costs.

Forgetting charges

After drawing out the arrows and determining what the alternative resonance structure will look like, leaving out a charge or two is an easy mistake to make (see Figure 3-29). One way to quickly check for missing charges is to see if all of your charges balance. That is, the net charge that you begin with must equal the net charge that you end up with. If your starting resonance structure has a net negative charge, then all other resonance structures must have a net negative charge as well.

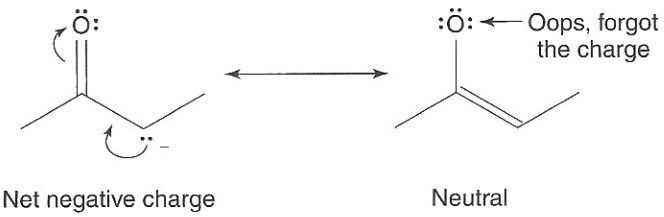


Figure 3-29: Keeping track of charges.

That's not to say that the *number* of charges must be the same, just that the net charge must be the same. For example, if you start with no charges on a resonance structure, an alternative resonance structure can end up with one positive charge and one negative charge, because the net charge remains zero. But starting with a neutral molecule and ending up with one negative charge or one positive charge is not acceptable. If you see that your charges don't balance, this generally indicates that you simply neglected to place a charge on one of the atoms.

Breaking the octet rule

Breaking the octet rule is a fairly common mistake, and, unfortunately, it's a big one. A general rule to remember is that an atom in the second row of the Periodic Table (like C, N, O, F) will never have more than eight electrons around it. This means that the sum of all the bonds and lone pairs around one of these atoms cannot total more than four. I've known professors who have threatened to flunk students if on the final exam they drew a pentavalent carbon (a carbon with five bonds) like the one shown in Figure 3-30. So avoid making this mistake.

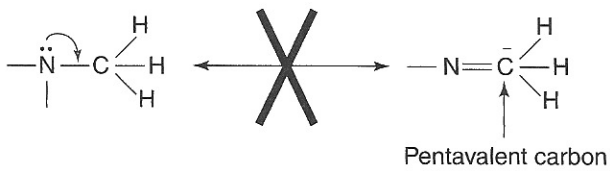


Figure 3-30: Pentavalent carbon. A major organic chemistry no-no.

Moving single bonds

Resonance structures involve the movement of only lone-pair and pi electrons. Therefore, you cannot move single bonds. To do so would break up a molecule into fragments, as shown in Figure 3-31.

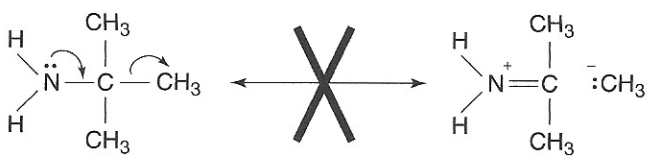


Figure 3-31: Single bond resonance — also a major no-no.

Not following the electron flow

Electrons are always drawn "flowing" in a single direction. So arrows won't start going one way and then double back in the opposite direction, as shown in Figure 3-32.

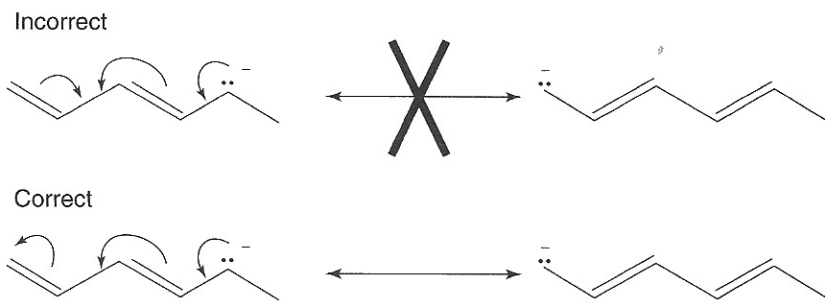


Figure 3-32: Resonance going against the flow.

Chapter 4

Covering the Bases (And the Acids)

In This Chapter

- Defining acids and bases
- Comparing acidities of organic molecules
- Seeing pKa values
- Predicting the directions of acid-base equilibria

You've surely done some acid-base chemistry in your lifetime, or at least observed some. Have you ever put lemon juice on fish to neutralize the fishy odors? Did you ever make a bottle rocket or fake volcano using baking soda and vinegar? Have you ever baked bread, cookies, or cakes? If so, then you've done acid-base chemistry. Certainly, you've dealt with acids and bases at some point. Foods such as tomatoes, oranges, lemons, sodas, and coffee are acidic, while household items such as bleach, ammonia, baking soda, and soaps are basic.

In fact, almost every reaction in organic chemistry involves acid-base chemistry — almost every one of them. Understanding how acids and bases work, therefore, is critical in understanding the reactions of organic molecules.

In this chapter, I define acids and bases using the three prominent definitions in use today. I show you how you can qualitatively predict the relative acidities of organic molecules by structural comparison, and I describe how organic chemists use a quantitative scale, called the pKa scale, to numerically define a molecule's acidity. I then show you how you can use this pKa scale to predict the direction of an acid-base reaction at equilibrium.

A Defining Moment: Acid-Base Definitions

Before I get to the nitty-gritty of how acids and bases work, I first need to define what they are. Three definitions are currently accepted for defining whether a molecule is an acid or a base: the Arrhenius definition, the Brønsted-Lowry definition, and the Lewis definition.

Arrhenius acids and bases: A little watery

Svante Arrhenius, a prominent chemist from the early twentieth century (whose ideas on acids and bases later earned him the Nobel Prize), defined acids as molecules that dissociate in water to make the hydronium ion, H_3O^+. Strong acids are those that completely dissociate in water to make hydronium ions, while acids that only partially dissociate in water are said to be weak acids. Nitric acid (HNO_3), shown in Figure 4-1, is a strong acid because it completely dissociates in water to make hydronium ions; acetic acid (CH_3COOH) only partially dissociates in water and is a weak acid. (The direction of the equilibrium in Figure 4-1 is shown with the larger arrow.)

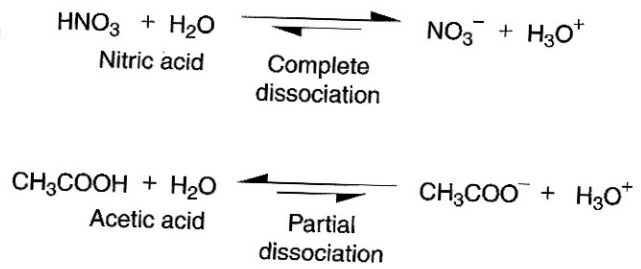


Figure 4-1: The dissociation of strong and weak acids.

Bases, on the other hand, are molecules that dissociate to make hydroxide ions, OH^-. As is the case with acids, bases that dissociate completely to generate hydroxide ions are strong bases, while bases that only partially dissociate to generate hydroxide ions are weak bases. Potassium hydroxide (KOH), shown in Figure 4-2, is a strong base because it completely dissociates in water to make hydroxide ions; beryllium hydroxide ($Be(OH)_2$) is a weak base because it only partially dissociates in water.

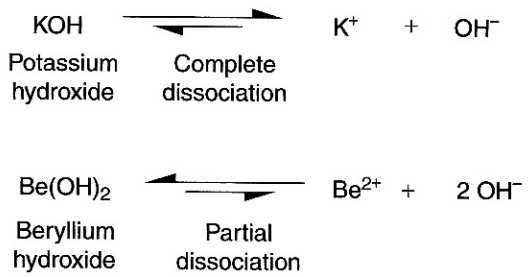


Figure 4-2: The dissociation of strong and weak bases.

Pulling for protons: Brønsted acids and bases

The Arrhenius definition, while useful, has some serious limitations. First, the definition cannot apply to all molecules, because many molecules are not soluble in water. Second, not all bases dissociate to generate the hydroxide ion. Ammonia (NH_3), for example, creates hydroxide ion in solution, but has no hydroxide ion in its formula, and so it's not a basic molecule by virtue of dissociation.

Therefore, other acid-base definitions that are more widely applicable are necessary. The most commonly used acid-base definition in organic chemistry is the Brønsted-Lowry definition of acids and bases. A *Brønsted-Lowry acid* is a molecule that donates a proton (H^+) to a base; a *Brønsted-Lowry base* is a molecule that accepts a proton from an acid.



An H^+ ion is called a proton because the hydrogen atom has no neutrons or electrons — just a single proton at the nucleus.

To keep the terminology straight, the deprotonated acid becomes what is known as the *conjugate base* (usually negatively charged, but not always), while the protonated base becomes the *conjugate acid,* as Figure 4-3 shows.

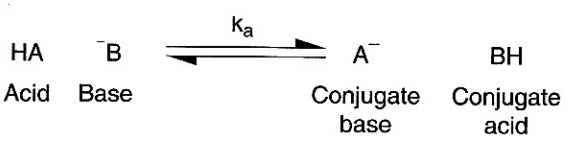


Figure 4-3: An acid-base reaction.

Electron lovers and haters: Lewis acids and bases

While the Brønsted-Lowry definition of acids and bases is more general than the Arrhenius definition, it still is not all-encompassing because it doesn't include molecules such as BF_3 or $AlCl_3$, which neither donate protons nor accept them. The most general method for classifying acids and bases is the Lewis acid and base definition. A *Lewis acid* is a molecule that accepts electrons, and a *Lewis base* is a molecule that donates electrons.

Borane (BH_3) is an example of a Lewis acid. Borane is a very unhappy molecule because it doesn't have a full octet of valence electrons (see Chapter 2 for an explanation of valence electrons). Because it doesn't have a full octet of electrons, it can accept a lone pair from a molecule like methylamine (CH_3NH_2), which has a lone pair of electrons, and use this electron pair to fill its octet (see Figure 4-4). Because BH_3 accepts electrons, it's said to be a Lewis acid; because methylamine donates electrons, it's said to be a Lewis base.

Lewis acids are also called *electrophiles*, which means "electron lovers." Lewis bases are also called *nucleophiles*, which means "nucleus lovers." You see the terms nucleophile and electrophile used repeatedly throughout organic chemistry courses.



Nucleophiles are molecules that can donate electrons (Lewis bases) and are nucleus lovers; electrophiles are molecules that can accept electrons (Lewis acids) and are electron lovers.

A word about acids and bases

It's easy to call a molecule an acid or a base, and say, "That's all there's to it, folks." But the terms "acid" and "base" are a little more elusive. A molecule is an acid only in comparison to another molecule, and likewise for a base. When the terms "acid" or "base" are used when discussing a particular molecule, they're used in comparison to a reference molecule — water. Water is capable of acting both as an acid and as a base, and any molecule that's more acidic than water is generally considered an acid, and any molecule that's more basic than water is generally considered a base.

But you should recognize that these terms are general. Most people would agree that nitric acid is an acid; its name even includes the word acid. But even nitric acid can act as a base under the right conditions! In the presence of the more acidic sulfuric acid, nitric acid acts as a base (you see this reaction in the nitration of benzene in Chapter 13). This reaction is an extreme case, but I hope it makes you wary of rigidly classifying a molecule as an acid or a base, even though doing so is convenient. Whether a molecule acts as an acid or as a base really depends on what is thrown into the reaction pot along with it.

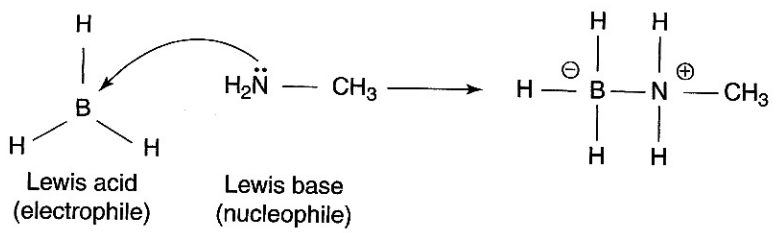


Figure 4-4: Lewis acids (electron acceptors) and Lewis bases (electron donors).

Lewis acids and bases encompass Brønsted acids and bases as well. Any Brønsted acid will also be a Lewis acid, and any Brønsted base will be a Lewis base (see Figure 4-5 for an example). One might reasonably ask, "If that's the case, why use Brønsted acids and bases at all?" The answer is that it's much more convenient for the organic chemist to think of acid-base reactions in terms of proton transfers rather than in terms of electron transfers. That's why when acids and bases are discussed in organic chemistry, with only a few exceptions, it's in terms of Brønsted acid and bases.

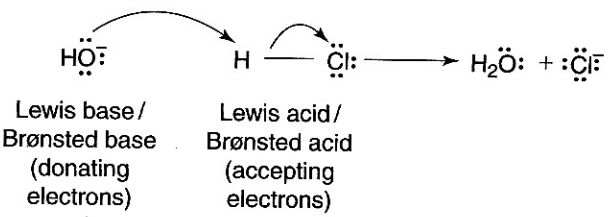


Figure 4-5: Brønsted acids are also Lewis acids.

Comparing Acidities of Organic Molecules

In general, the strength of an acid is directly proportional to the stability of the acid's conjugate base. In other words, an acid that has a more stable conjugate base will be more acidic than an acid that has a less stable conjugate base. Because the conjugate base is usually negatively charged (anionic), a convenient tactic when comparing the acidities of molecules is to think about what structural features in a molecule contribute to stabilizing negative charges. The more stable these negative charges are, the more acidic the acid is. In the sections that follow, I talk about structural features that stabilize negative charges and lead to stronger acids.



Strong acids have stable conjugate bases.

In general, acidic molecules have structural features that allow the anion in the conjugate base to delocalize the charge. Delocalization of the negative charge (such that one atom doesn't have to bear the full negative charge) makes the molecule more stable. The three most important features that stabilize negative charges include the electronegativity, hybridization, and size of the atom upon which the negative charge is located, the electron-withdrawing effects of neighboring electronegative atoms, and resonance effects.

Comparing atoms

On which atom does the negative charge of the acid's conjugate base rest? A negative charge prefers to rest on electronegative (electron-loving) elements. Therefore, a negative charge is more stable on oxygen than it is on nitrogen; similarly, a negative charge is more stable on nitrogen than it is on carbon. For that reason, alcohols (R—OH) are more acidic than amines (R—NH_2), which in turn are more acidic than alkanes (R—CH_3), as shown in Figure 4-6.

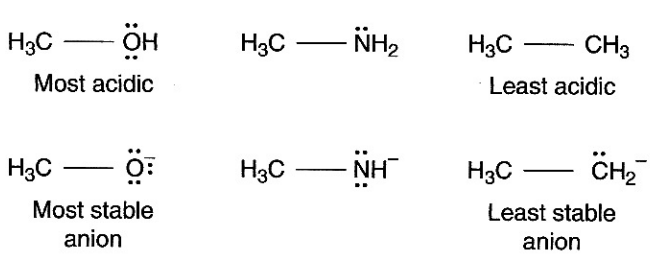


Figure 4-6: Negative charges prefer to rest on the more electronegative atoms.



Electronegativity increases as you go up and to the right on the Periodic Table.

The size of the atom also plays a role in stabilizing the negative charge. Charges prefer to be on larger atoms than on smaller atoms. This preference results from large atoms allowing the negative charge to delocalize over a much larger region of space, rather than being concentrated in a small region (as it would on a small atom). As a rule, atom size trumps electronegativity

considerations. So even though fluorine is a more electronegative atom than iodine, HI is more acidic than HF. The much larger iodine atom allows the negative charge to delocalize over a larger space than does the much smaller fluorine atom, and thus makes hydrogen iodide more acidic. The effect that atom size has on acidity is shown in Figure 4-7.

H — F	H — Cl	H — I
acid		Strongest acid
F^-	Cl^-	I^-
Least stable		Most stable

Seeing atom hybridization

The orbital that the lone pair anion rests on also affects the acidity. Lone pair anions prefer to reside in orbitals that have more *s* character than *p* character, because *s* orbitals are closer to the atom's nucleus than *p* orbitals, and the electrons are stabilized by being closer to the nucleus. Orbitals that are *sp* hybridized have 50 percent *s* character, orbitals that are sp^2 hybridized have 33 percent *s* character, and orbitals that are sp^3 hybridized have 25 percent *s* character. Therefore, anions prefer to be in orbitals that are *sp* hybridized over those that are sp^2 hybridized orbitals, and they prefer to be in orbitals that are sp^2 hybridized over those that are sp^3 hybridized. The effect of orbital type on acidity is shown in Figure 4-8 (refer to Chapter 2 to read more about orbital hybridization).

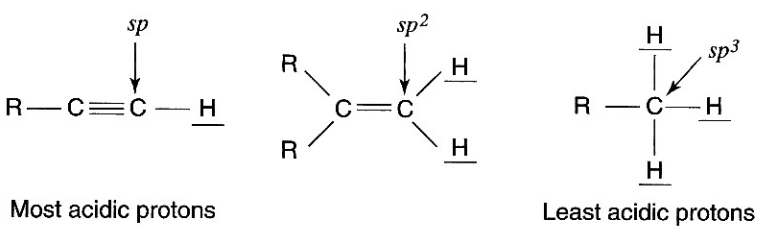
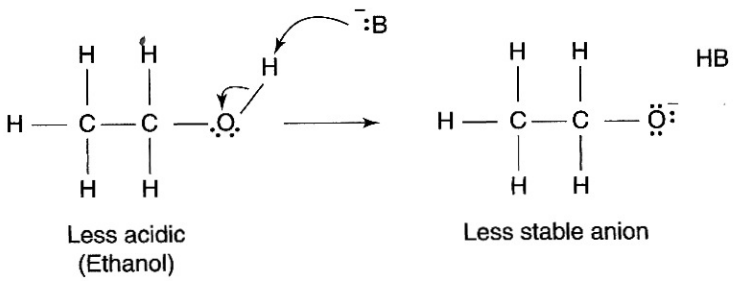


Figure 4-8: The types of orbitals affect acidity.

Seeing electronegativity effects

Electron-withdrawing groups on an acid also stabilize the conjugate base anion by allowing some of the charge on the anion to delocalize to other parts of the molecule. For example, trifluoroethanol (shown in Figure 4-9) is more acidic than ethanol. The highly electronegative fluorine atoms (which attract electrons) on trifluoroethanol pull electron density away from the anion, taking away some of the negative charge from the oxygen, thereby stabilizing the molecule.



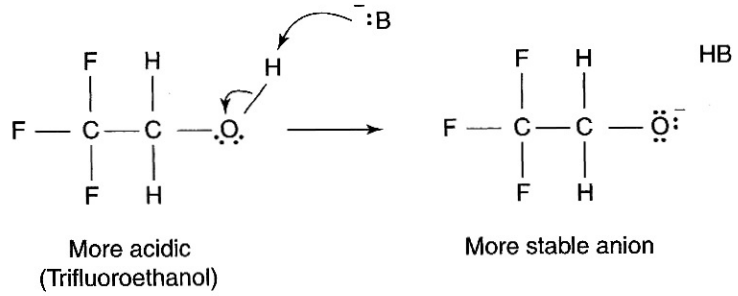


Figure 4-9: Electron-withdrawing groups add to a molecule's acidity.

Seeing resonance effects

Acids with conjugate bases that allow the negative charge to be delocalized through resonance are stronger acids than acids whose conjugate bases don't have resonance structures. For example, acetic acid, shown in Figure 4-10, is much more acidic than ethanol because the conjugate base anion of acetic acid can delocalize the negative charge through resonance.



Resonance structures are a stabilizing feature of molecules.

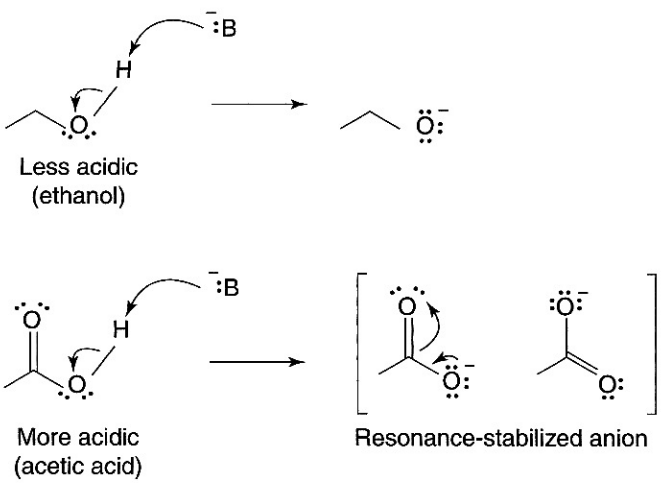


Figure 4-10: Resonance effects contribute to acidity.

Defining pKa: A Quantitative Scale of Acidity

The pKa value of an acid is a quantitative measurement of a molecule's acidity. The pKa is derived from the rate constant for the acid's dissociation, Ka, and uses a logarithmic scale to allow the pKa values to span wide ranges.

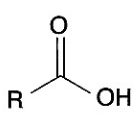
$$Ka = \frac{[A^-][BH]}{[HA][B^-]} \qquad pKa = -\log Ka$$



The lower the pKa value of an acid, the stronger the acid. The higher the pKa value, the weaker the acid. Very strong acids have pKa values of less than zero, while weak acids generally have pKa values of between zero and nine.

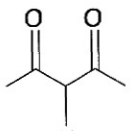
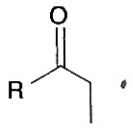
A brief pKa table of acids is shown in Table 4-1.

Table 4-1 Approximate pKa Values of Common Acids

Acid	*Approximate pKa*	*Acid*	*Approximate pKa*
H_2SO_4	–7	H_3O^+	–2
HCN	9		5

(continued)

Table 4-1 *(continued)*

Acid	*Approximate pKa*	*Acid*	*Approximate pKa*
			
R–OH	16		10
			
	20	CH_4	50

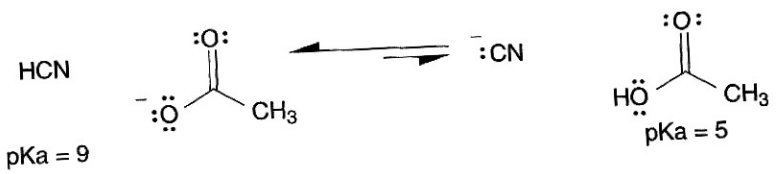
Problem Solving: Predicting the Direction of Acid-Base Reactions at Equilibrium

With pKa table in hand (or in your memory, if your professor insists upon it), you can predict the equilibrium direction of acid-base reactions. Weak acids and bases are lower in energy than strong acids and bases, and because equilibria favor the reaction side with the lowest-energy species, acid-base reactions will go to the side with the weakest acids and bases.



As a rule, the equilibrium of a reaction will favor the side with weaker acids and bases.

For example, you can predict the direction of the acid-base reaction between hydrogen cyanide (HCN) and acetate ($C_2H_3O_2^-$) shown in Figure 4-11. Because hydrogen cyanide (pKa = 9) has a higher pKa value than acetic acid (pKa = 5), the equilibrium will lie to the left, in the direction of the weaker acid and base. That's really all there is to predicting the direction of an acid-base reaction. If you know the pKa values of the two acids on both sides of the equation, then you know in which direction the equilibrium lies, because equilibrium will favor the side with the acid that has the highest pKa.


HCN
pKa = 9
:O:
:O
CH3
:CN
:O:
HO
CH3
pKa = 5

Chapter 5

Reactivity Centers: Functional Groups

- functional groups

▶ Finding functional groups in nature

Consider this: Millions of reactions of organic molecules are currently known, and that number is getting bigger by the day. That's probably a scary thought. Can you imagine trying to learn all of them? The good news is that you don't have to learn all of the reactions of specific molecules because organic molecules often react in predictable ways based on what kinds of groups a particular molecule contains.

Alkanes — molecules containing just singly bonded hydrogen and carbon atoms — are pretty much inert under most conditions. Carbon, though, is unique among the elements in that it has the capability of forming stable compounds that have multiple bonds to other carbons, in addition to stable bonds to other non-carbon atoms, forming reactive centers. These reactive centers are called *functional groups* and are the reactive portions in a molecule. Chemists organize organic compounds based on what functional groups are present in a particular molecule.

One reason learning the functional groups is important is that if you learn the general reactions of a particular functional group, you have essentially learned the reactions of thousands of specific molecules that contain that functional group. This is the reason that the naming of organic molecules is based on what functional groups are present in a molecule, because the functional groups dictate how a molecule will react. Thus, the sooner you memorize these functional groups, the better.

In this chapter, I present the most important functional groups that you encounter throughout organic chemistry. I give examples of natural sources in which these molecules are found to show their relevance to biological systems. Additionally, I discuss their commercial uses, general nomenclature points, and interesting properties. This overview, I hope, will help you remember these functional groups and will give you a feel for the uses of particular functional groups.

Hydrocarbons

Hydrocarbons, as the name suggests, are molecules that contain just hydrogen and carbon. Simple hydrocarbons are generally cheap and commercially available, because they are found as components in crude oil. Hydrocarbons include alkanes (which contain only single bonds and are generally not considered a functional group), alkenes (molecules containing carbon-carbon double bonds), and aromatics (double-bonds containing ring systems).

Double the fun: The alkenes

An *alkene* is a molecule that contains a carbon-carbon double bond (see Chapter 2 for more on double bonds). The general form of an alkene is shown in Figure 5-1. (See Chapter 3 for an overview of molecular drawings.)

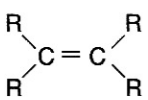


Figure 5-1: The general form of an alkene.



The R is an abbreviation for the Rest of the molecule. An R group most often implies a hydrogen atom or a hydrocarbon group. It is used when a generality is being demonstrated, or when the rest of the molecule is not very important in understanding what is being discussed.

Alkenes are often found in natural products, compounds isolated from living organisms. In the simplest alkene, ethylene, each R group is a hydrogen atom (see Figure 5-2). Ethylene is a gaseous plant hormone that is released when

the plant reaches maturity, signaling that it's time for the fruit to start ripening. Farmers often have special equipment that they use to spray ethylene on their crops when they want to force the fruit to ripen.

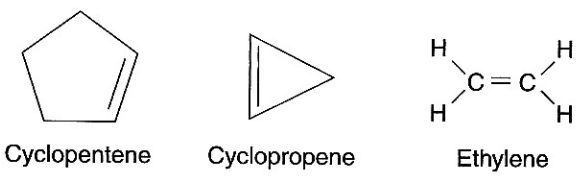


Figure 5-2: The structures of some common alkenes.

Alkenes are also used commercially. Ethylene *polymerizes* (combines many small units to make large molecules) to make polyethylene — a molecule formed from many ethylene molecules strung one after another to form a big chain. Polyethylene is a type of plastic used in containers such as grocery bags, milk bottles, and many different items that you see and use every day.

Alkenes can even be arranged in rings, like with cyclopropene, although they generally don't like to be in very small rings like cyclopropene (see Figure 5-2). I talk about alkenes in Chapter 8.

Alkenes are particularly important to organic chemists because they can be transformed into many different functional groups. They are easily made and converted into other things; this makes them particularly useful as a go-between in the synthesis of complex molecules. In this book, I show how alkenes are converted into alkanes, cycloalkanes, cyclic ethers, alcohols, alkyl halides, aldehydes, and carboxylic acids. That's versatile!

The names of alkenes generally end with the suffix "ene." One particularly important alkene is Vitamin A (a.k.a. retinol). Vitamin A (see Figure 5-3) is an organic compound that contains five double bonds. It is important in vision, protects against sickness, and is used in skin care products as an antioxidant that protects the skin from free radicals suspected of causing premature aging of the skin. (Read more about free radicals in Chapter 7.) I discuss the reactions, properties, and nomenclature of alkenes in detail in Chapter 8.

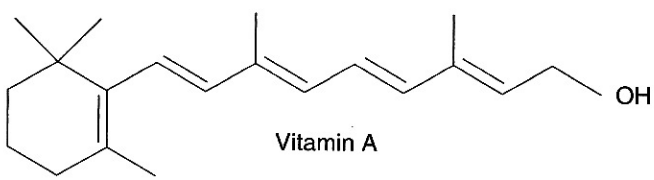


Figure 5-3: The structure of Vitamin A (retinol).

Alkynes of fun

Alkynes are molecules that contain a carbon-carbon triple bond. See Figure 5-4. Many of their reactions and properties are similar to those of the alkenes, although the chemistry of alkenes and alkynes has some interesting differences.

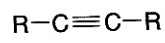


Figure 5-4: The general form of an alkyne.

The simplest alkyne, acetylene, has the two R groups substituted with hydrogen (Figure 5-5). Acetylene is a gas that is used as a welding fuel, and usually smells of garlic because of impurities contained in it. Because acetylene burns cleanly and produces a very hot flame, acetylene torches reach temperatures of over 3,000°C, hot enough to weld metals, melt glass, and scorch off your pinkies if you aren't careful. Other common alkynes include methyl acetylene (or propyne) and dimethyl acetylene (or 2-butyne); see Figure 5-5 for the structures of these alkynes.

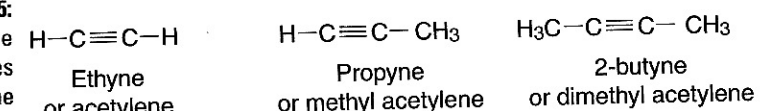
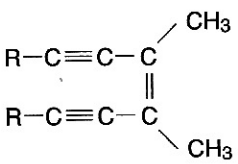


Figure 5-5: The structures of some common alkynes.

Alkynes are less common than alkenes in nature, but they do pop up occasionally. Calicheamicin (try saying that three times fast), for example, is a complicated organic molecule that is made by a bacterium that grows in rocks. Calicheamicin was recently found to selectively attack and kill the DNA of cancer cells, and has, along with similar compounds, been used as a drug in anticancer therapies.



The biologically active portion of the calicheamicin molecule contains two triple bonds (see Figure 5-6). This portion is called an ene-diyne — the "diyne" part of the name means "two ynes," or "two triple bonds"; can you guess where the "ene" portion of the name comes from?



Calicheamicin

Figure 5-6: The structure of calicheamicin.

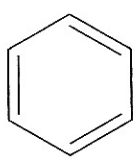
Alkynes prefer to have bond angles of 180°, where the triple bond and the two R groups on either side lie in a straight line. Triple bonds aren't particularly stretchy, and because of this, molecules with triple bonds are generally unstable in rings of fewer than eight carbons.

Alkynes end with the suffix "yne." Sometimes, they are called by the common name that derives from the simplest alkyne, acetylene. I cover the specifics of alkyne properties and reactions in Chapter 9.

Smelly compounds: The aromatics

The *aromatics* (or *arenes*, as they're often called) consist of rings containing double bonds. The principal aromatic compound is benzene, a six-carbon ring containing three alternating double bonds (see Figure 5-7). You might think that benzene would behave like a ring containing three alkenes. This turns out not to be the case. Aromatic compounds have a special property that makes them significantly more stable, and less reactive, than alkenes. In Chapter 13, I discuss why benzene and other aromatics are so stable, and also talk about aromatic compounds other than benzene.

These rings are called aromatics because the first of these compounds to be discovered (even before their structures were determined) had funky smells. Benzene itself is found as a component in crude oil, and even has better burning properties than does the octane fuel that you use to top off your gas tank. Unfortunately, it is a carcinogen and has other undesirable properties, so it is not used as a fuel. However, it is often used by organic chemists (with careful handling) as a solvent and as a cheap starting material in multistep syntheses.



Benzene

Figure 5-7: The structure of benzene.

Many compounds made by living organisms contain aromatic rings. (See Figure 5-8 for the structures of some aromatic compounds; see Chapter 6 for more on 3-D structure.) Morphine, for example, contains a benzene ring that is vital to its pain-relieving properties. Auto exhaust, soot, and tobacco smoke contain fused rings of benzene, like benzopyrene, where the rings are squished together to make very large aromatic compounds. These compounds have been found to be carcinogenic. In fact, chimney sweeps (the guys who used to clean chimneys in the days when coal was used for home heating) had remarkably high incidence of testicular cancer because of their high exposure to these aromatic compounds in the chimney soot.

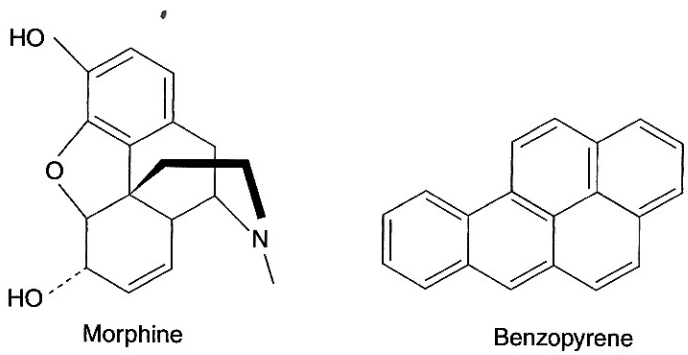


Figure 5-8: The structures of some aromatic compounds.

Singly Bonded Heteroatoms

Heteroatoms refer to atoms other than carbon or hydrogen. These heteroatoms include such important atoms as the halogens, oxygen, and sulfur, and are the components of the halide, alcohol, ether, and thiol functional groups. Each of these functional groups is described in this section.

Happy halides

The *halides* are organic compounds that contain one or more halogens. (Halogens are those elements found in column 7A of the Periodic Table.) The four halogens that you frequently see in organic compounds are fluorine, chlorine, bromine, and iodine. The general form of a halide is shown in Figure 5-9.

Halides, like alkynes, are seldom found in natural products, and when they are found, they are often in compounds that are toxins. Commercially, halides are used as propellants in aerosol cans such as hair spray and spray paint, and as refrigerants. Evidence that certain alkyl halides (that is, halides attached to alkanes) persist in the atmosphere and that these compounds contribute to depleting the ozone layer has led many countries to limit or outlaw their use as propellants. An example of a refrigerant halide is shown in Figure 5-10.

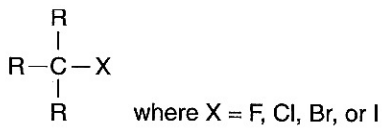


Figure 5-9: The structure of a simple halide.

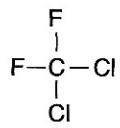


Figure 5-10: The structure of a refrigerant.

Halides are also used as insecticides. For example, DDT (dichlorodiphenyltrichloroethane; see Figure 5-11) was widely used to protect crops from insects, until evidence suggested that this compound accumulated in the environment and caused unwanted side effects in wildlife, like the thinning of the eggshells of wild birds, and the death of bats and rodents. In large enough doses DDT was even found to cause death to humans. So, as much as we may dislike bats and rodents, this compound had to go, and this compound is now banned in the United States.

Other halides are still used in homes and businesses. For example, Teflon is a fluorine-containing polymer used in non-stick surfaces like pots and pans. See Figure 5-11. The brackets with the *n* subscript in the structure of Teflon indicate that portion of the molecule is a repeating unit.

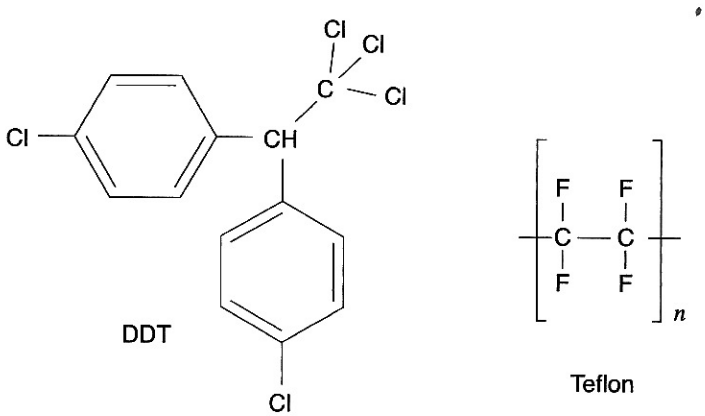


Figure 5-11: The structures of some common halides.

Many other halides are important to organic chemists because they are good thruways to other molecules; they are easily made and converted into other things. I talk more about halides and their reactions in Chapter 10.

For rubbing and drinking: Alcohols

Alcohols are also a very common and important group of organic compounds. *Alcohols* consist of the general formula R-OH, and have names that end with the suffix "ol." Probably the alcohol you're most familiar with is ethanol (or ethyl alcohol) as it's the alcohol found in beer, wine, and liquor. Ethanol is toxic in large enough doses, and some of its effects include a decrease in your body's motor coordination, lowered inhibition, loud and off-key karaoke singing, and crank calls to your mother-in-law. Simple alcohols, such as isopropanol (rubbing alcohol), are used in cleaning solutions and as disinfectants, and an alcohol with two OH groups, ethylene glycol (which is also toxic, so don't let your dog drink it), is used in antifreeze. Figure 5-12 illustrates some common alcohols.

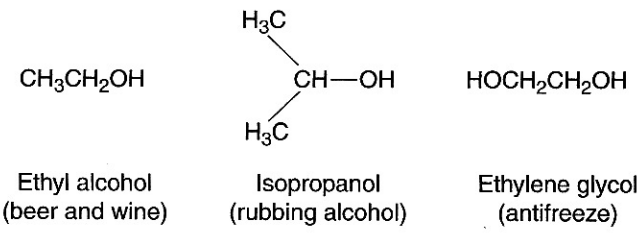
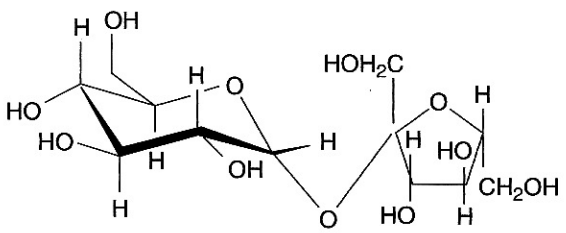


Figure 5-12: The structures of some common alcohols.

Alcohols are also commonly found in natural products. Sugars, for example, like the table sugar sucrose shown in Figure 5-13, contain many OH groups.



Sucrose (table sugar)

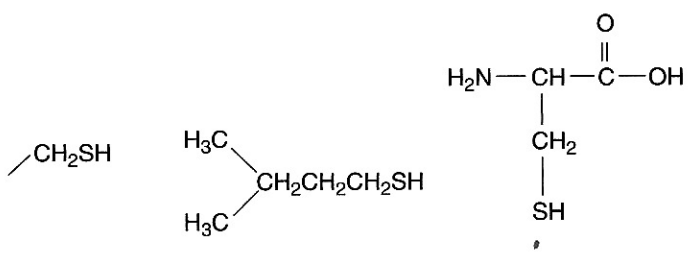
Figure 5-13: The structure of table sugar (sucrose), showing the fructose and glucose components.

What stinks? Thiols

Very few organic chemists have a burning desire to work with thiols. That's because *thiols* are foul-smelling compounds, of the general formula R-SH. Thiols are the sulfur analog of alcohols, and are often hideously unpleasant compounds. Certain thiols, for example, are found in skunk spray — that stinky stuff skunks use to fend off predators. Other thiols are responsible for the odors in flatulence, garlic, sewage, and rotten eggs. Commercially, very small amounts of thiols are added to methane gas so you can detect when a gas line has sprung a leak (methane itself is odorless).

Not all thiols are associated with such unpleasantries, however. Cysteine, for example, is one of the amino acids that the human body uses to produce proteins, and this amino acid plays a particularly important role in keratin, a protein found in hair. These cysteine amino acids (see Figure 5-14) are important because they can couple with each other and make disulfide bonds (S-S bonds) that hold the shape of your hair. If you've ever had a perm, you experienced thiol chemistry. A perm involves treating the hair with chemicals and heat to break the disulfide bonds, reshaping the hair in the desired way, and then resetting the disulfide bonds.

Generally, names of thiols end with the suffix "thiol," as is the case with two of the thiols found in skunk spray, 2,3-dimethyl-2-buten-1-thiol and 3-methyl-1-butanethiol, both of which are shown in Figure 5-14.



2,3-dimethyl-2-buten-1-thiol | 3-methyl-1-butanethiol | Cysteine

How ethereal

Ethers are molecules containing an oxygen sandwiched between two carbons (see Figure 5-15). Molecules containing ether functional groups are widely used as solvents in organic reactions. Additionally, before it was replaced by modern anesthetics that make recovery less painful, diethyl ether (commonly

known as "ether") was used as an anesthetic to knock patients unconscious for surgery. Ethers found in three-membered rings are given the specific name *epoxide*. Epoxides are found in epoxy resins and in epoxy glues, and are common as intermediates in multistep syntheses.

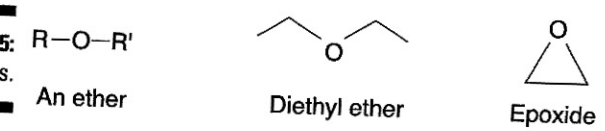


Figure 5-15: Ethers.

Carbonyl Compounds

The chemistry of living things is largely the chemistry of carbonyl compounds. A *carbonyl group* is a C=O group — in other words, a carbon atom double-bonded to oxygen. A carbonyl group is not considered a functional group in itself; instead, it's considered a component in some of the most important functional groups, including the aldehydes, ketones, esters, amides, and carboxylic acids. If you're considering taking a course in biochemistry, you should have a good understanding of the reactions and properties of carbonyl compounds because most of the reactions in the body are carbonyl reactions (including the reactions in the Krebs Cycle, in glycolysis, and in the synthesis of fatty acids and polyketides).

Living on the edge: Aldehydes

Aldehydes are the simplest of the carbonyl compounds. In an *aldehyde* (see Figure 5-16), the carbonyl group is flanked by one hydrogen and one R group. It might be helpful to think of an aldehyde as a carbonyl group at the end of an organic molecule.

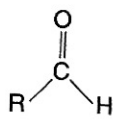
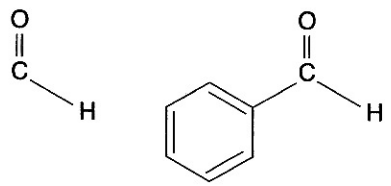


Figure 5-16: An aldehyde.

The simplest aldehyde, formaldehyde — in which the R group is hydrogen — has many uses including as a preservative. Often the smells that waft from a biology laboratory come from the formaldehyde used to preserve specimens

(not that chemists have much right to complain, though, considering some of the smells emitting from their laboratories). Retinal is a large aldehyde; it is one of the pigments that traps light in the eyes of humans, making vision possible. Benzaldehyde is a wonderfully sweet-smelling compound that gives almonds its odor. Both retinal and benzaldehyde are shown in Figure 5-17.



Retinal Benzaldehyde

You'll often see aldehydes represented as R-CHO. Don't confuse this condensed form with an alcohol, which is represented as R-OH.

Stuck in the middle: Ketones

Compounds that contain a carbonyl group sandwiched between two carbons are called *ketones*. If an aldehyde can be thought of as a carbonyl at the end of a molecule, then a ketone is a carbonyl somewhere in the middle of a molecule. The simplest ketone, in which both R groups are CH_3 units, is called acetone, a common laboratory solvent. Acetone is the smelly stuff found in nail polish remover, and is the reason why polished nails don't stay polished for very long in organic laboratories. The names of ketones generally end with the suffix *-one*.



e of A ketone Acetone

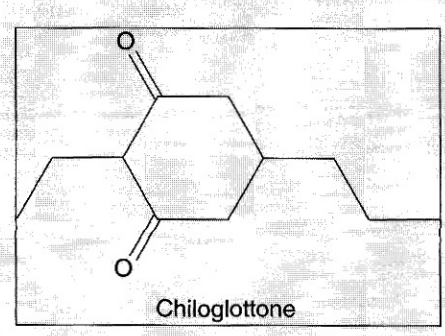
Sneaky orchids, ketones, and chemical siren songs

In 2003, German and Australian scientists first reported their discovery of the *diketone* (a molecule with two ketone functional groups) chiloglottone, produced by an Australian orchid flower. This orchid, they discovered, uses this diketone to reproduce, to get its pollen to another orchid for pollination. But how, you ask, can a chemical be responsible for transporting the orchid's pollen to another orchid, sometimes over several miles? By trickery, deception, and bamboozling, of course. This deception forms yet another interesting episode of the soap opera between plants and insects, a soap opera that mostly goes undetected by humans.

Chiloglottone, it turns out, not only is produced by the Australian orchid, but also is the sex pheromone of a species of wasp native to Australia. When a female wasp emits this pheromone, she signals to all eligible male wasps in the area that she is ready to mate. When a male wasp detects the pheromone in the air, it does the equivalent of a wasp "hubba hubba hubba," and wastes no time in tracing the chemical trail back to its source for a little wasp hanky panky. The orchid, however, has cracked the chemical code of communication between the wasps, and takes advantage of their instant messaging system for its own devious purposes. The orchid makes its mischief by producing and transmitting the same sex pheromone that the wasps produce, and uses the chemical as a lure.

When they detect the pheromone produced by the orchid, the wasps — in typical male fashion — are so swooned by the possibility of wasp love that they become irrational, and in the height of their passion they neglect to realize that the orchid is not a female wasp, and, in fact, is not a wasp at all. Swooping down, the male wasp tries his best to mate with the orchid's flower head, and when he's finished his business, he flies away from the orchid with a thin dusting of orchid pollen on his legs. Coated with pollen, the wasp flies off until he is attracted by another orchid emitting the sex pheromone, and, feeling amorous yet again, he "mates" with the second orchid. When the pollen from the first orchid rubs off of the wasp's legs, the second orchid becomes pollinated.

In this way, the orchid tricks the male wasp into becoming a postman for its pollen, free of charge, no stamps required. This kind of bamboozling is actually quite common in nature, and is called *sexual deception*. Though insects get revenge in some ways on plants — munching on them, for instance! — this round belongs to the plants.



Chiloglottone

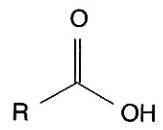
Carboxylic acids

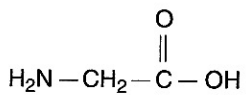
The *carboxylic acid* functional group is made up of a carbonyl group attached to an OH group. The general form of carboxylic acids is shown in Figure 5-19.

Don't confuse a carboxylic acid with a ketone or an alcohol. Carboxylic acids have entirely different properties and reactivities than either ketones or alcohols. In particular, the proton (H^+) on the oxygen in a carboxylic acid is unusually acidic (hence the name!), for reasons I talk about in Chapter 4.

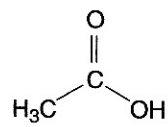
Carboxylic acids are abundant in nature. In fact, each of the amino acids that our body uses as building blocks to make proteins contains a carboxylic acid (such as the amino acid glycine in Figure 5-19), as do all of the fatty acids. The names of carboxylic acids generally end with *–oic acid,* like ethanoic acid (more commonly called acetic acid), which is the carboxylic acid responsible for the flavor and bitterness of vinegar.

ac ds.





Glycine (an amino acid)

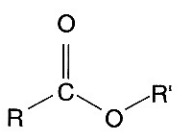


Acetic acid (vinegar)

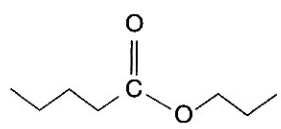
Sweet-smelling compounds: Esters

Esters are very similar in structure to carboxylic acids. An *ester* is basically a carboxylic acid with the hydrogen sniped off, and an R group glued in its place. (In fact, esters are made from carboxylic acids.) Esters are generally sweet-smelling compounds, and many of the lovely smells from fruits are esters. (See Figure 5-20 for the structures of some esters.) Because of this, they are generally found in deodorants and as artificial flavorings in food. The names of esters generally end with the suffix *-oate*.

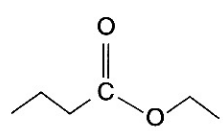
esters.



An ester



Propyl pentanoate (pineapples)



Etyl butanoate (apples)

Nitrogen-containing functional groups

Just as the carbonyl compounds play an important role in nature, so do nitrogen-containing compounds. Illicit drugs and painkillers, which are often *alkaloids* (nitrogen-containing rings) often contain nitrogen as well.

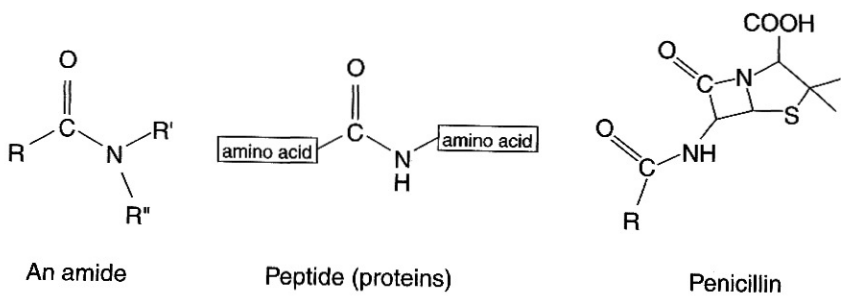
Even though the primary component in air is nitrogen gas (N_2), most plants and animals cannot use this as a source of nitrogen because in its gaseous state nitrogen is so unreactive and stable. The N_2 gas needs to be converted to ammonia (NH_3) or nitrate (NO_3^-) for animals and plants to be able to use it as a building block, a process called nitrogen fixation. This job is left up to microorganisms, which have special enzymes that can tackle this reaction. (Lightning strikes also account for some nitrogen fixation, although only a small amount.)

I am what I amide

Amides are close relatives of esters, except that amides have a nitrogen (rather than an oxygen) next to the carbonyl group. Amides are quite often found in nature. *Amide bonds* hold all of our proteins together (the amide bond in proteins is called a *peptide bond*). See Figure 5-21 for the structures of some common amides.



The famous antibiotic Penicillin contains two amide groups. The amide in the four-membered ring (called a β-*lactam ring*) is responsible for penicillin's bacteria killing properties; this amide group ruptures the cell walls of bacteria. (For more about penicillin, see Chapter 19.)

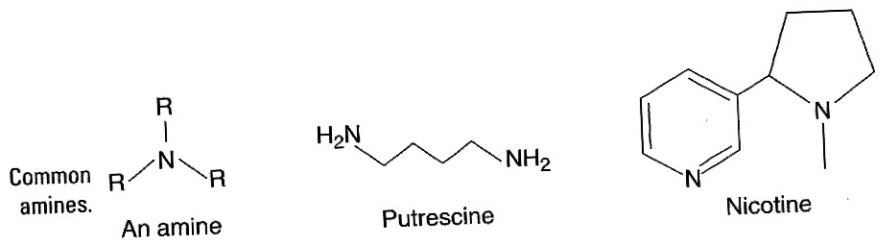


An amide | Peptide (proteins) | Penicillin

Figure 5-21: The general structure of an amide and a peptide, and the specific structure of penicillin.

Be nice, don't be amine person

Amines are nitrogen atoms that take the place of a carbon atom in an alkane (the three forms of an amine are R-NH_2, R_2NH, or R_3N). Amines are not known for their pleasantness. For example, the smell of decaying animals comes from the *diamine* (a molecule with two amine functional groups) putrescine, for example. So you probably don't want to use these compounds as perfumes. Plants and animals and other organisms make many important amine compounds. Nicotine (see Figure 5-22), as well as many other familiar compounds like cocaine, mescaline, amphetamine, and morphine are all amine-containing compounds. Unfortunately, amine compounds are often abused; most illegal drugs contain amines that are essential to the drug's activity.



Nitriles

Nitriles are compounds that contain a carbon triply bonded to nitrogen. Nitriles aren't terribly important in natural products, but they are useful in organic synthesis. Nitriles can be converted into carboxylic acids and amines by well-known procedures. Acetonitrile, in which the R group is a methyl group (CH_3), is a common organic solvent. Nitriles generally end with the suffix "nitrile" and as substituents on a molecule they are referred to as *cyano* groups. See Figure 5-23.

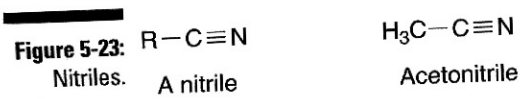


Figure 5-23: Nitriles.

Test Your Knowledge

Figure 5-24 gives you a made-up molecule that contains some of the functional groups that I've mentioned in this chapter. How many can you identify? (***Hint:***

Draw out all of the condensed portions — like COOH, CN, and CHO — to help you identify which functional group it is.)

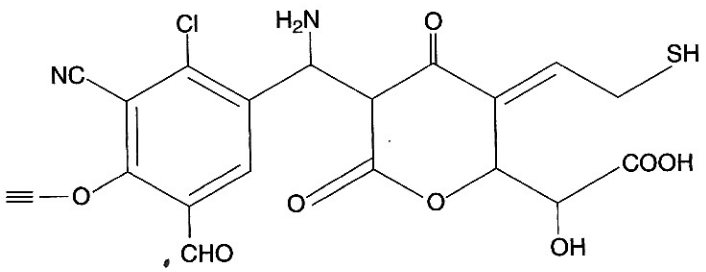


Figure 5-24: A hypothetical molecule with different functional groups.

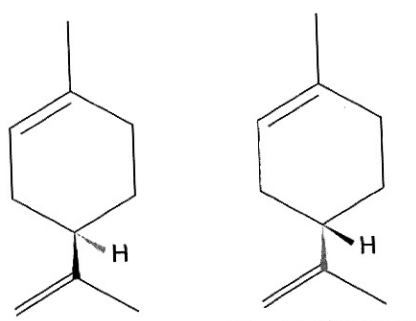
Chapter 6

Seeing in 3-D: Stereochemistry

In this chapter, you look closely at molecules in three dimensions. Why should you care about the arrangements of atoms in three-dimensional space? Because nature does. Virtually all of the compounds produced in nature — proteins, sugars, carbohydrates, DNA, and RNA, to name just a few — have atoms oriented in very specific ways in three-dimensional space.

Subtle differences in the way molecules are arranged in three-dimensions can be recognized, for instance, by your nose receptors. Limonene, for example, shown in Figure 6-1, can have two different three-dimensional configurations (solid wedges indicate a bond coming out of the plane of the paper; dashes indicate a bond going back into the paper). If the molecule is arranged in one configuration, it smells of oranges; arranged in the other configuration it smells of lemons!

rations



Smells of lemons

This discrimination by your nose receptors (of molecules differing only in the orientation of atoms in three-dimensional space) is fairly common in biological systems. Most drugs, in fact, are only active when they have a very specific three-dimensional configuration, while compounds with an identical structure but with different arrangements of the atoms in space are usually completely ineffective, or even harmful. (See the "Biological importance of stereochemistry: The thalidomide tragedy" sidebar later in this chapter for an example of such harmful drugs.) Because of this biological significance of the three-dimensionality of molecules, the study of stereochemistry — the way that molecules orient themselves in three-dimensional space — is very important, particularly in the pharmaceutical industry.

Drawing Molecules in 3-D

To be able to study stereochemistry, you need to be able to draw three-dimensional molecules on a two-dimensional piece of paper. When you draw molecules in three-dimensions, you typically use solid and dashed wedges. A solid wedge (▬) indicates a bond coming out of the plane of the piece of paper, and a dashed wedge (▬) indicates a bond going back into the paper. A regular line (—) indicates a bond that's in the same plane of the paper. When you want to draw an sp^3 carbon atom (see Chapter 2) in three dimensions, you draw two bonds in the plane of the paper, one bond coming out of the plane of the paper, and one bond going back (behind the plane of the paper), in a tetrahedral arrangement (see Figure 6-2).

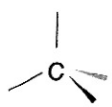


Figure 6-2: Tetrahedral arrangement.

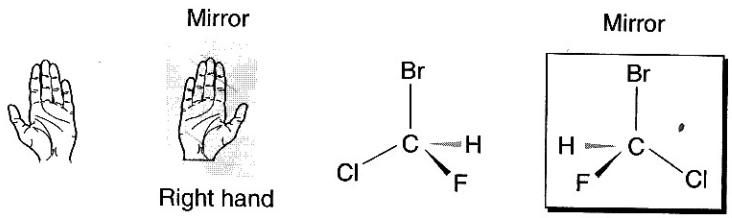
Comparing Stereoisomers and Constitutional Isomers

The two different limonene molecules shown in Figure 6-1 are *stereoisomers*. Stereoisomers are different than constitutional isomers. Constitutional isomers are molecules with the same molecular formula but with atoms connected to each other in different ways (see Chapter 7). Stereoisomers, on the other hand, are molecules with the same atom connectivity but with different orientations of those atoms in space.

Your hands, for example, are stereoisomers. On both hands, all of your fingers are attached in the same way — thumb, index finger, middle finger, ring finger, and pinky, in that exact order. But although your hands have the same finger connectivity, your hands are not identical — they are stereoisomers of each other. Try putting a right-handed glove on your left hand if you don't believe me; it won't work. If you happen to be an alien with one hand having a pinky where a thumb should be and a thumb where a pinky should be, then your hands would be constitutional isomers, because the connectivity of your fingers would be different.

Image Molecules: Enantiomers

Molecules that are nonsuperimposable mirror images of each other are called *enantiomers.* Your right hand is the enantiomer of your left hand because your hands are mirror images of each other (put your right hand up to a mirror, and you'll see what looks like a left hand). Enantiomers cannot be superimposed onto each other, just as your right hand cannot be superimposed on your left hand. To translate this feature to structures, the compound shown in Figure 6-3 cannot be superimposed on its mirror image; if you slide the compound over its mirror image, the various parts of the two molecules won't line up. You might try making the molecular models of the two enantiomers to prove to yourself that you can't superimpose these enantiomers over each other — the atoms simply don't align.



If you really want to grasp stereochemistry, you need to mess around with molecular models. When you play with models, you get a feel for stereochemistry in your bones, not just in your head.

Molecules that are not superimposable on their mirror images (like the halogenated methane shown in Figure 6-3) are said to be *chiral* molecules (hard k sound, rhymes with viral). Conversely, molecules that *can* be superimposed on their mirror images are said to be *achiral.* Methane (Figure 6-3) is an example of an achiral molecule. Methane is superimposable on its mirror image.

That is, if you rotate the mirror image of methane, the atoms superimpose (or overlap) on the original molecule perfectly. Thus, methane doesn't have an enantiomer because its mirror image is identical to itself.

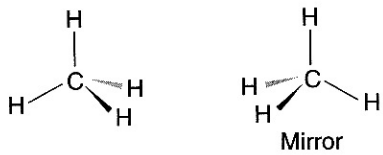


Figure 6-4: Methane: An achiral molecule.



Only chiral molecules have enantiomers.

Seeing Chiral Centers

How can you tell whether a molecule will be chiral or achiral without constructing the molecule's mirror image and seeing if the two can be superimposed? Most often, chiral molecules contain at least one carbon atom with four nonidentical substituents. Such a carbon atom is called a *chiral center* (or sometimes a *stereogenic center*), using organic-speak. Any molecule that contains a chiral center will be chiral (with one exception, discussed later). For example, the compound shown in Figure 6-5 contains a carbon atom with four nonidentical substituents; this carbon atom is a chiral center, and the molecule itself is chiral, because it's nonsuperimposable on its mirror image.

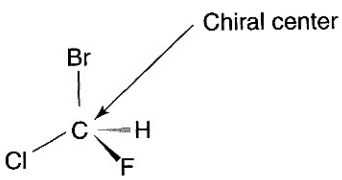


Figure 6-5: A chiral center.

You need to be able to quickly spot chiral centers in molecules. All straight chain alkyl group carbons (CH_3 or CH_2 units) will *not* be chiral centers because these groups have two or more identical groups (the hydrogens) attached to the carbons. Neither will carbons on double or triple bonds be chiral centers because they can't have bonds to four different groups. When looking at a molecule, you should look for carbons that are substituted with four different

groups. See, for example, if you can spot the two chiral centers in the molecule shown in Figure 6-6.

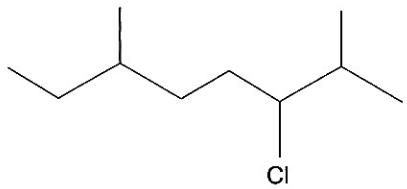


Figure 6-6: A molecule with two chiral centers.

Because all CH_3 and CH_2 groups cannot be chiral centers, the molecule shown in Figure 6-5 has only three carbons that can be chiral centers. While the two leftmost possibilities, identified in Figure 6-7, have four nonidentical groups and are chiral centers, the one on the far right has two identical methyl (CH_3) groups and so is not a chiral center.

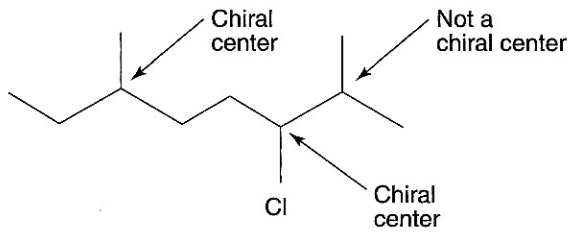


Figure 6-7: The chiral centers in a long molecule.

Assigning Configurations to Chiral Centers: The R/S Nomenclature

Any chiral center can have two possible configurations (just as a hand can have two configurations, either right or left), and these configurations are designated either R or S by convention (the terms R and S come from the latin words for right and left, *rectus* and *sinister*). If a molecule has a chiral center that is designated R, the chiral center will be S in the molecule's enantiomer.

You need to be able to assign whether a chiral center is R or S. To do so, you need to follow three steps. They are as follows:

1. **Number each of the substituents on the chiral center carbon using the Cahn-Ingold-Prelog system.** This numbering scheme is conveniently the

same one used in determining E/Z stereochemistry on double bonds, as described (in more detail) in Chapter 9. According to the Cahn-Ingold-Prelog prioritizing scheme, the highest priority goes to the substituent whose first atom has the highest atomic number. (For example, Br would be higher priority than Cl, because Br has a larger atomic number.) If the first atoms on two substituents are the same, you keep going down the chain until you reach a larger atom and the tie is broken.

2. **After you've assigned priorities to each of the substituents, rotate the molecule so that the number-four priority substituent is oriented in the back.**
3. **Draw a curve from the first priority substituent through the second priority substituent and then through the third.** If the curve goes clockwise, the chiral center is designated R; if the curve goes counter-clockwise, the chiral center is designated S.

Problem Solving: Determining R/S Configuration

To get the hang of applying R/S nomenclature to chiral centers, you need lots of practice. Try to determine the R/S stereochemistry of the chiral center in the molecule shown in Figure 6-8.

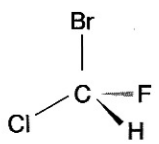


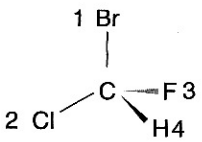
Figure 6-8: A chiral molecule.

Step 1: Prioritizing the substituents

The first step is to prioritize all of the substituents from one to four. Bromine is the atom with the largest atomic number, so this substituent is given the highest priority; hydrogen has the smallest atomic number and so is given the lowest priority. Chlorine gets the number two priority because it's bigger than fluorine, which is given priority three. The priorities are shown in Figure 6-9.

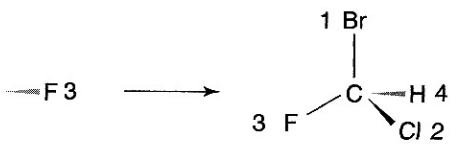


Hydrogen will always be given the lowest (fourth) priority.



Step 2: Putting the number-four substituent in the back

The next step is to rotate the molecule so that the number four substituent is pointed toward the back, as shown in Figure 6-10. For many people, this is the most difficult step because to rotate the molecule requires visualizing the molecule in three dimensions.



If you're not good at visualizing in three dimensions, you can use some tricks to put the number four priority group in the back without having to mentally rotate the molecule in three-dimensional space.

Here are the tricks. First, swapping any two substituents changes the configuration — that is, if the chiral center was R before the swap, it becomes S after the swap (and vice-versa). So if you swap the number four substituent with the substituent located in the back, as shown in Figure 6-11, the configuration of the chiral center switches. After you've made the switch to put the number four priority substituent is in the back, you could then go to step three and determine the configuration, remembering that the actual configuration of that center is the opposite of the one determined.

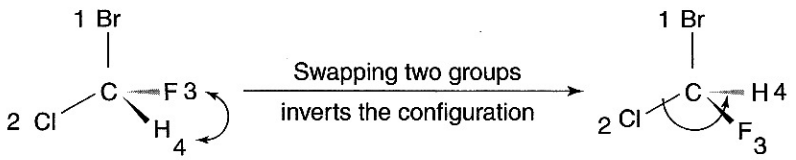


Figure 6-11: Swapping two groups in a chiral center.

Or you could keep going, swapping two more positions. While swapping the positions of the first two substituents inverts the configuration, swapping the remaining two substituents after you perform this operation reverts the configuration back to the one you started with, as shown in Figure 6-12. So, if you first swap the number four substituent with the group in the back, and then swap the remaining two substituents, you get two inversions of the configuration, which amounts to a net retention of the configuration. (For example, if the chiral center starts R, and you invert two substituents, it becomes S; if you invert two more substituents, the configuration goes back to R.) Doing this double swap is an easy way of getting the number four priority substituent into the back without doing mental rotations of the atoms.

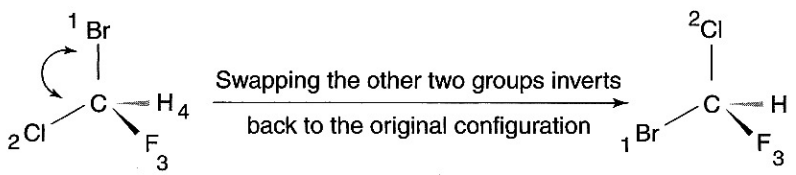


Figure 6-12: Swapping two more groups in a chiral center.



Swapping the positions of two substituents inverts the configuration.

Step 3: Drawing the curve

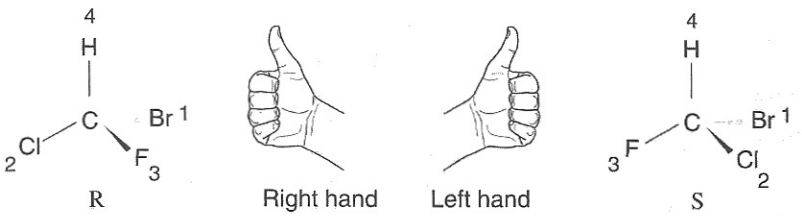
Now that the number four priority substituent is in the back, you draw a curve from the first priority substituent through the second priority substituent, to the third priority substituent. In this case, the curve goes clockwise, so the molecule has R stereochemistry, as shown in Figure 6-13.



If the fourth priority substituent is in front, you can just reverse the rules of the last step and cut out step three. With the number four substituent in front, a clockwise curve from the first to the third priority substituents results in an S configuration; a counterclockwise curve would indicate an R configuration.

All thumbs: An alternative technique for assigning R and S stereochemistry

A very convenient way to determine the R/S configuration of a chiral center is with the thumb technique. With this technique, shown in the accompanying figure, you point your thumb in the direction of the number four priority substituent. If, with your thumb pointed toward the fourth priority substituent, the fingers in your right hand can curl in the direction from the first to second to third priority substituent in that order, the configuration is R; if you must use your left hand to get your fingers to curl from the first to second to third priority substituent, then the configuration is S. The main advantage of this technique is that you don't have to put the number four priority substituent into the back; you just point your thumb in whatever direction the number four priority substituent is facing.



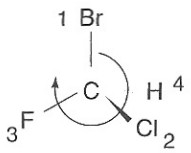


Figure 6-13: The R stereochemistry.

The Consequences of Symmetry: Meso Compounds

Any molecule that contains a chiral center will be chiral, with one exception: Those molecules that contain a plane of symmetry will be achiral, regardless of whether the molecule has a chiral center. A plane of symmetry is a plane that cuts a molecule in half, yielding two halves that are mirror reflections of each other.

Recall that by definition, a molecule that's not superimposable on its mirror image is a chiral molecule. While compounds that contain chiral centers are generally chiral, molecules that have planes of symmetry are achiral, and have structures that are identical to their mirror images. Molecules that contain chiral centers but are achiral as a result of having a plane of symmetry are called *meso* compounds, using organic speak. For example, cis-dibromo cyclopentane shown in Figure 6-14 is meso because a plane cuts the molecule into two halves that are reflections of each other. Trans-dibromo cyclopentane, however, is chiral because no plane splits the molecule into two mirror-image halves.

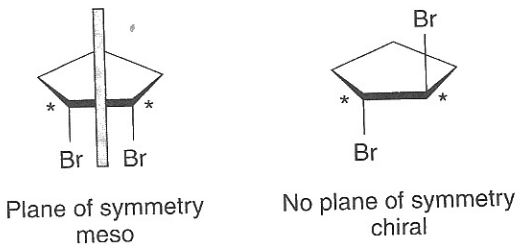


Figure 6-14: The plane of symmetry in meso compounds.

Look at the mirror images of these two molecules (shown in Figure 6-15) to prove this generality to yourself. Even though the cis compound has two chiral centers (indicated with asterisks), the molecule is achiral because the mirror image is identical to the original molecule (and is therefore superimposable on the original molecule). Molecules with planes of symmetry will always have superimposable mirror images and will be achiral. On the other hand, the trans stereoisomer has no plane of symmetry, and is chiral.

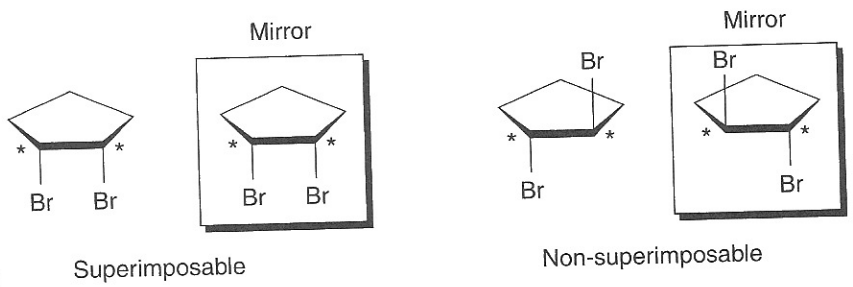


Figure 6-15: The mirror images of achiral (meso) and chiral molecules.



Meso compounds are achiral.

In organic chemistry, you need to be able to spot planes of symmetry in molecules so you can determine whether a molecule with chiral centers will be chiral or will be meso. For example, can you spot the planes of symmetry in each of the meso compounds shown in Figure 6-16?

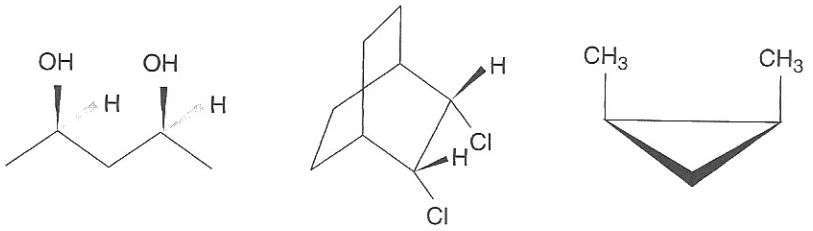


Figure 6-16: Some meso compounds.

Rotating Plane-Polarized Light

Enantiomers share nearly all physical properties with each other — they have the same boiling points, melting points, dipole moments, and all other properties, save one. Enantiomers rotate plane-polarized light in opposite directions. Light waves propagate in all directions, and plane-polarized light is simply light that has been filtered to allow only light propagating in one direction to pass through the filter (this is the way that many sunglasses work to block out light). When plane-polarized light is passed through a sample containing a chiral molecule, the light is rotated either to the right or to the left by a certain number of degrees (labeled α), as shown in Figure 6-17.

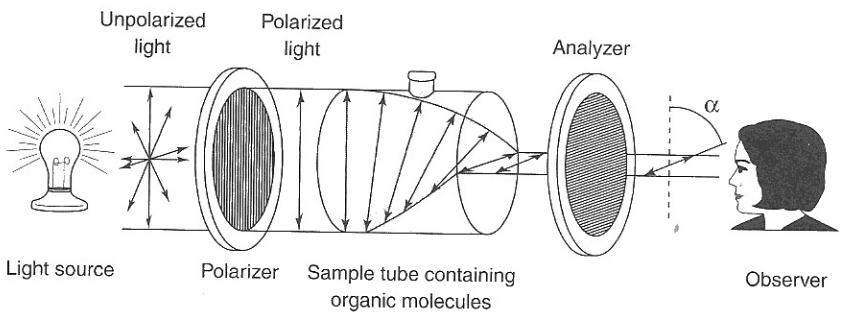


Figure 6-17: A polarimeter.



Only chiral molecules rotate plane-polarized light. The number of degrees that a chiral molecule rotates the light must be determined by experiment and is not something that you can figure out on your own. The direction of light rotation by a molecule is not something you can determine from looking at the structure of a molecule either (R or S designation does not tell you which way the light will be rotated). However, if you know that a chiral molecule rotates light by 30°, then you know its enantiomer will rotate plane-polarized light by exactly –30° (that is, 30° in the opposite direction).



Enantiomers rotate plane-polarized light in equal and opposite directions.

If you mix two enantiomers in equal proportions, you get a *racemic mixture* — a 50:50 mix of enantiomers. Racemic mixtures do not rotate plane-polarized light. This is because half of the molecules in the mix rotate the light one direction, and the other half of the molecules rotate the light the other direction, resulting in a net rotation of zero. Such racemic mixtures are therefore said to be *optically inactive,* which means that they don't rotate plane-polarized light.

Multiple Chiral Centers: Diastereomers

When only one chiral center exists in a molecule, the only possible stereoisomer is the enantiomer, the molecule's mirror image. But when more than one chiral center is present in a molecule, you have the possibility of having stereoisomers that are not mirror images of each other. Such stereoisomers that are not mirror images are called *diastereomers.*



Typically, you can only have diastereomers when the molecule has two or more chiral centers.

The number of possible stereoisomers that a molecule can have is a function of 2^n, where n is the number of chiral centers in the molecule. Therefore, a molecule with five chiral centers can have 2^5 or 32 possible stereoisomers! As the number of chiral centers increases, the number of possible stereoisomers for that compound increases rapidly.

For example, the molecule shown in Figure 6-18 has two chiral centers.

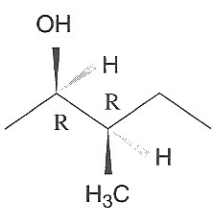


Figure 6-18: A molecule with two chiral centers.

Because this molecule has two chiral centers, this molecule can have a total of 2^2, or four, possible stereoisomers, of which only one will be the enantiomer of the original molecule. Because both chiral centers in this molecule are of R configuration, the enantiomer of this molecule would have the S configuration for both chiral centers. All of the stereoisomers of this molecule are shown in Figure 6-19. Those molecules that are not enantiomers of each other are diastereomers of each other.

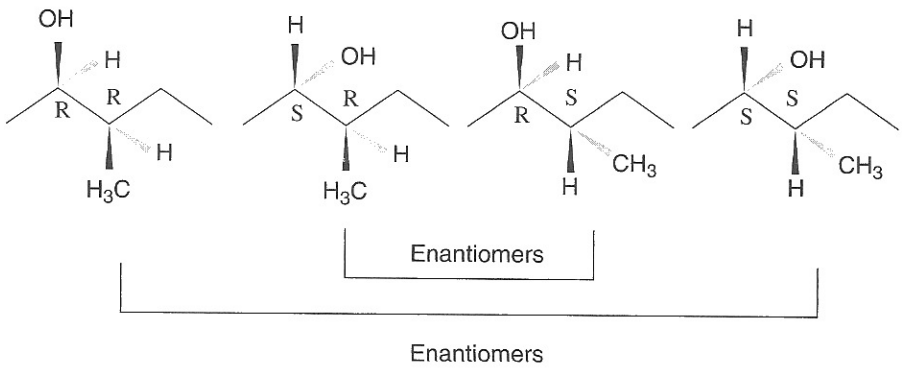


Figure 6-19: The four stereoisomers of a molecule with two chiral centers.

Representing 3-D Structures on Paper: Fischer Projections

The most convenient way of viewing molecules with more than one chiral center is with Fischer projections. A Fischer projection is a convenient two-dimensional drawing that represents a three-dimensional molecule. To make a Fischer projection, you view a chiral center so that two substituents are coming out of the plane at you, and two substituents are going back into the plane, as Figure 6-20 shows. Then the chiral center becomes a cross on the Fischer projection. Every cross on a Fischer projection is a chiral center.

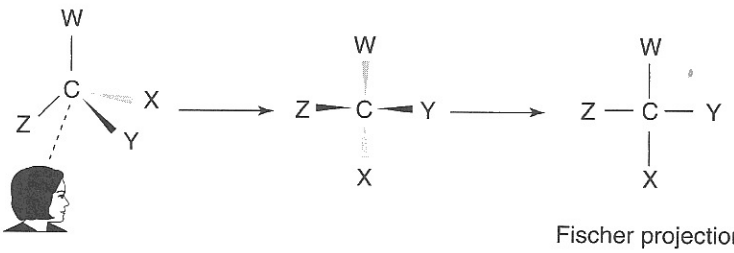


Figure 6-20: Creating a Fischer projection.

Rules for using Fischer projections

Fischer projections are convenient for comparing the stereochemistries of molecules that have many chiral centers. But these projections have their own sets of rules and conventions for how you can rotate and move them. The two main ways to rotate a Fischer projection are as follows:

- You can rotate a Fischer projection 180° and retain the stereochemical configuration, but you cannot rotate a Fischer projection 90° (see Figure 6-21).
- You can rotate any three substituents on a Fischer projection while holding one substituent fixed and retain the stereochemical configuration.

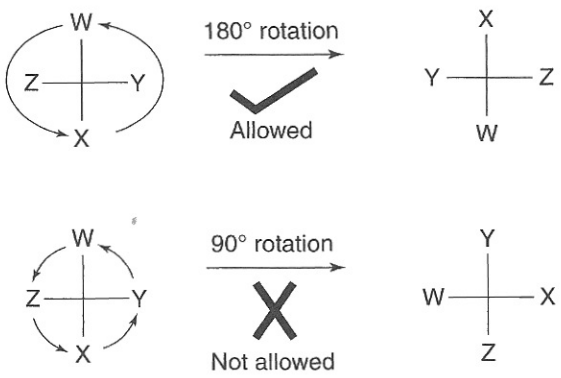


Figure 6-21: Working with Fischer projections.

Determining R/S configuration from a Fischer projection

Here's how to determine the configuration of a chiral center drawn in a Fischer projection. First, you prioritize each of the substituents using the Cahn-Ingold-Prelog prioritizing scheme. (This is the same prioritizing scheme used in a previous section of this chapter and discussed in detail in Chapter 8.) Then, you put the fourth priority substituent on the top, and draw a curve from the first to the second to the third priority substituent. If the curve goes clockwise, the configuration is R, if the curve goes counterclockwise, the configuration is S. To get the number four priority substituent at the top of the Fischer projection, you have to use one of the two allowed moves diagramed earlier in Figure 6-21. (You can make a 180° rotation, or you can hold one substituent fixed and rotate the other three.) Two examples of the determination of the configuration from Fischer projections are shown in Figure 6-22.

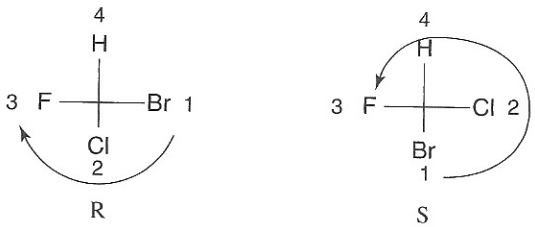


Figure 6-22: Determining R and S configurations from Fischer projections.

Seeing stereoisomerism with Fischer projections

One of the main advantages of Fischer projections is that you can easily see the relationships between stereoisomers. In other words, with a Fischer projection, you can quickly determine whether two stereoisomers are diastereomers or enantiomers. For example, the relationships between some stereoisomers of a molecule are shown in Figure 6-23. When you compare stereoisomers, you want to make sure that the tops and bottoms are lined up correctly. In other words, when comparing two Fischer projections, make sure that both projections have the same top and the same bottom, and that one isn't upside down (if one is upside down, do an allowed 180° rotation). After the tops and bottoms are oriented correctly, you compare the directions of the substituents between the two molecules at every cross on the Fischer projection. A substituent that points to the left in a Fischer projection will point to the right in its enantiomer.

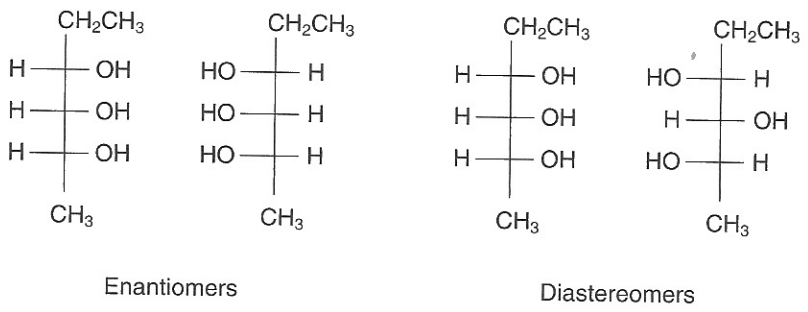


Figure 6-23: Seeing the relationships between stereoisomers in Fischer projections.

Spotting meso compounds with Fischer projections

Another convenient feature of Fischer projections is that you can often spot meso compounds more easily with Fischer projections than you can with molecules drawn out with dashes and wedges. With the Fischer projection, the symmetry of the molecule is easier to spot. An example of symmetry in a Fischer projection is shown in Figure 6-24.

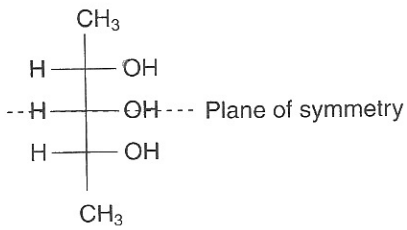


Figure 6-24: The Fischer projection of a meso compound.

Keeping the Jargon Straight

One of the most confusing aspects of stereochemistry is the massive amount of new terminology that you need to remember. So here's a mini glossary of stereochemical terminology to keep you straight:

- **Achiral molecule:** An achiral molecule is one that can be superimposed over its mirror image; an achiral molecule is identical to its mirror image. Achiral molecules do not rotate plane-polarized light.
- **Chiral center:** Typically, for a molecule to be chiral it must have at least one chiral center — a carbon with four nonequivalent groups. These chiral centers are assigned either R or S configuration. Any molecule that contains a chiral center will be chiral, unless the molecule has a plane of symmetry, in which case the molecule is achiral (and meso).
- **Chiral molecules:** A chiral molecule is one that cannot be superimposed over its mirror image. Chiral molecules rotate plane-polarized light.
- **Diastereomers:** Diastereomers are stereoisomers that are not mirror images of each other. For a molecule to have a diastereomer, it must typically have more than one chiral center.
- **Enantiomers:** Molecules that are mirror images of each other are called enantiomers.
- **Meso compounds:** A meso compound is a molecule that contains a chiral center, but is achiral as a result of having a plane of symmetry in the molecule.

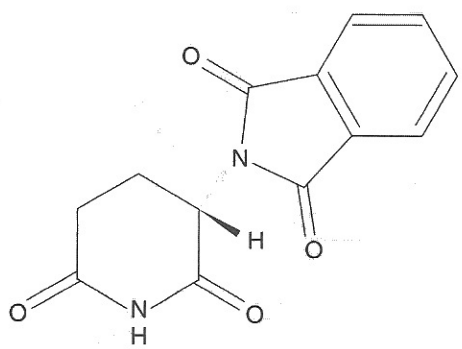
- **Optically active:** An optically active compound (such as a pure solution of a single enantiomer of a molecule) has the ability to rotate plane-polarized light.
- **Racemic mixtures:** A racemic mixture is a 50:50 mixture of two enantiomers. Racemic mixtures do not rotate plane-polarized light.

Biological importance of stereochemistry: The thalidomide tragedy

Thalidomide, a chiral compound whose structure is shown in the accompanying figure, was a drug prescribed to pregnant women in Europe to counter the symptoms of morning sickness. Even though only one of the enantiomers of thalidomide actively worked against preventing morning sickness, the drug was prescribed as the racemic mixture (a 50:50 mix of both enantiomers).

Why was the drug dispensed as the racemic mixture rather than as the single active enantiomer? For practical reasons. Usually, selectively synthesizing one enantiomer over another is very difficult, and with most reactions that produce compounds with chiral centers, you get products that are racemic mixtures. Racemic mixtures are fiendishly difficult to separate because enantiomers share important physical properties. They have the same boiling points, so they can't be separated by distillation; they have the same dipole moments and solubilities so they can't be separated by recrystallization. Separating enantiomers is possible, but the task is often tedious and costly.

Unfortunately, while one enantiomer of thalidomide controlled the symptoms of morning sickness, the other enantiomer caused terrible side effects, including severe defects (like stunted limb growth) in the unborn children. The drug was pulled from the market when scientists discovered that these birth defects were caused by the drug. Since then, drugs have been required to undergo much better animal testing for possible side effects. (Thalidomide had been tested in mice, but not in rabbits or monkeys, which are closer biological relatives to humans.)



Thalidomide

Part II
Hydrocarbons



"I love this time of year when the organic chemistry students start exploring new and exciting ways for bonding carbon atoms."

In this part . . .

I exhume the bones of organic molecules — the hydrocarbons. Hydrocarbons are molecules that contain only hydrogen and carbon, and include the alkanes (molecules with only single bonds), the alkenes (molecules with carbon double bonds), and the alkynes (molecules with carbon triple bonds). In this part, you start to craft your skills in the nomenclature of organic molecules, and you get your first sampling of chemical reactions, which is a staple throughout the rest of organic chemistry. You also get a taste for *stereochemistry* — the different ways that atoms can orient themselves in three dimensions.

Chapter 7

The Bones of Organic Molecules: The Alkanes

In This Chapter

- Seeing the structures of alkanes
- Mastering alkane nomenclature
- Analyzing the conformations of alkanes
- Seeing alkane reactions

In this chapter, I cover the skeletons of organic molecules — the alkanes. Alkanes are the simplest organic molecules. Because they're the simplest of the organic molecules, they're useful for introducing several key principles in organic chemistry, such as *isomerism* (molecules with the same molecular formula but different structures), *conformation* (the different ways atoms can flex and bend), and *stereochemistry* (the orientation of atoms in three-dimensional space). Also, because alkanes make up the simplest organic molecules, they're the best place to start honing your skills in *nomenclature* (the rules for naming organic molecules).

Alkanes are compounds that contain only carbon-hydrogen single bonds. Because they have the maximum possible number of hydrogens, alkanes are said to be *saturated hydrocarbons*. Alkanes have the molecular formula of C_nH_{2n+2}, where n is the number of carbons in the molecule. An alkane that has eight carbons, for example, would have a molecular formula of C_8H_{18}.

What's in a Name? Alkane Nomenclature

Naming molecules is an important skill to have. Unlike biology, where organisms are given seemingly arbitrary names, organic molecules are named systematically. Once you understand the nomenclature rules and how to apply

them, you can name most molecules you come across. And thank goodness for that, as there are *millions* of known organic compounds. Can you imagine the amount of memorization that would be required if each one were given some arbitrary name? I don't even want to *think* about it.

Furthermore, every unique molecule in chemistry *must* have a different name. George Foreman may be able to name each of his five sons George Foreman Jr., but in chemistry, if two molecules are different, then they must have different names.

All in a line: Straight-chain alkanes

The names of alkanes all end with the suffix *-ane*. The prefixes for alkanes with one, two, three, and four carbons come from historical roots, while alkanes with more than five carbons have prefixes that derive from Greek (see Table 7-1). These prefixes simply must be memorized. The mnemonic, "**M**ary **e**ats **p**eanut **b**utter" may help you remember the prefixes for the first four alkanes that have historical roots — **m**ethane, **e**thane, **p**ropane, and **b**utane. After that, knowing the Greek numbers (for example, knowing that *hex* refers to six, and *oct* refers to eight) makes the names more familiar.

Table 7-1 The Names of the Straight-Chain Alkanes

Number of Carbons	*Name*	*Structure*
1	Methane	CH_4
2	Ethane	CH_3CH_3
3	Propane	$CH_3CH_2CH_3$
4	Butane	$CH_3(CH_2)_2CH_3$
5	Pentane	$CH_3(CH_2)_3CH_3$
6	Hexane	$CH_3(CH_2)_4CH_3$
7	Heptane	$CH_3(CH_2)_5CH_3$
8	Octane	$CH_3(CH_2)_6CH_3$
9	Nonane	$CH_3(CH_2)_7CH_3$
10	Decane	$CH_3(CH_2)_8CH_3$
11	Undecane	$CH_3(CH_2)_9CH_3$
12	Dodecane	$CH_3(CH_2)_{10}CH_3$

Reaching out: Branching alkanes

Oh, if life were only that simple! All of the alkanes in Table 7-1 have carbon atoms that are joined in a line, and so are called *straight-chain alkanes.* Alkanes, though, are not limited to staying in a line, and can have structures that branch. For example, the alkane with the formula C_4H_{10} can have two possible structures (see Figure 7-1) — one alkane that's a straight chain (butane), and one alkane that's branched (isobutane).

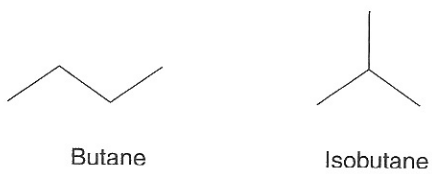


Figure 7-1: The isomers of C_4H_{10}.

Molecules that have the same molecular formula but different chemical structures are referred to as *isomers,* using organic-speak. Branching makes the nomenclature of these molecules a bit more difficult, but these branching molecules can still be named systematically. With a bit of practice, you'll soon get the hang of naming all alkanes — including branched ones — and nomenclature questions on exams will become gimmes.

Several steps need to be followed in order to name a branched alkane. In each of the following sections, I detail how to perform each step, using an example to clarify what I mean as I go along.

Finding the longest chain

The first, and potentially the trickiest, step is to find the longest chain of carbon atoms in the molecule. This task can be tricky because, as a reader of English, you're so used to reading from left to right. Often, however, the longest chain of carbons is not the chain that follows simply from left to right, but one that snakes around the molecule in different directions. Organic professors like to make the parent chain one that curves around the molecule and doesn't necessarily flow from right to left, so you have to keep on your toes to make sure that you've spotted the longest carbon chain.

The longest carbon chain for the molecule shown in Figure 7-2 is seven carbons long, so the parent name for this alkane is heptane (refer back to Table 7-1).

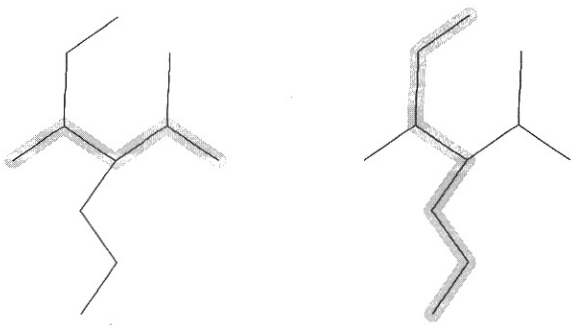


Figure 7-2: The right and wrong ways to count the parent chain.

Numbering the chain

Number the parent chain starting with the end that reaches a substituent first. A chain can always be numbered in two ways. In the case of the molecule in Figure 7-2, the numbering could start at the top and go down, or it could start at the bottom and go up. The correct way to number the parent chain is to start with the end that reaches the first substituent sooner. A *substituent* is organic-speak for a fragment that comes off of the parent group. In this example, if you number from the top down, the first substituent comes at carbon number three (see Figure 7-3); if you number bottom-up, the first substituent comes at carbon number four. The correct numbering in this case, then, starts at the top and goes down.

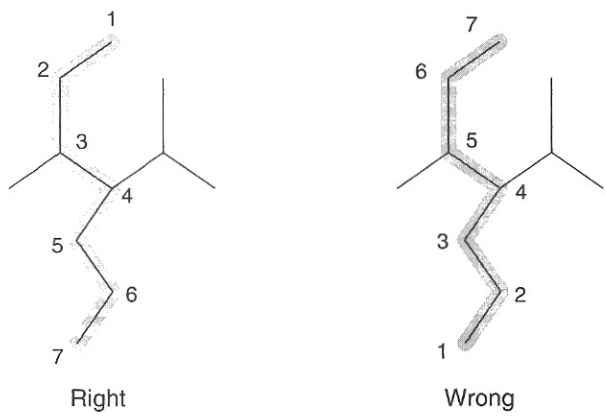


Figure 7-3: The right and wrong ways to number the carbons of the parent chain.

Seeing the substituents

After numbering the parent chain, the next step is to determine the names of all of the substituents that stick off of the parent chain. On this molecule, two substituents come off of the parent chain — one substituent at carbon number three, and one substituent at carbon number four (see Figure 7-4). Substituents are named in the same manner as the parent chains, except that instead of ending with the suffix *-ane* they end with the suffix *-yl,* which indicates that the group is a substituent off of the main chain. For example, the one-carbon substituent at carbon number three is a *methyl* substituent (not a meth*ane* substituent). A two-carbon substituent would be *ethyl*, a three-carbon substituent would be *propyl*, a four-carbon substituent would be *butyl*, and so on (refer back to Table 7-1).

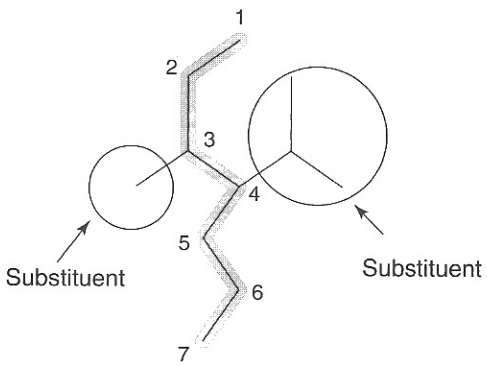


Figure 7-4: The locations of substituents on a parent chain.

Some substituents have common names rather than systematic ones. These simply must be memorized. The most important common substituents are the isopropyl group (a three-carbon group that looks like a snake's tongue), the tert-butyl (or t-butyl) group (that looks like a trident),,and the sec-butyl group, shown in Figure 7-5.

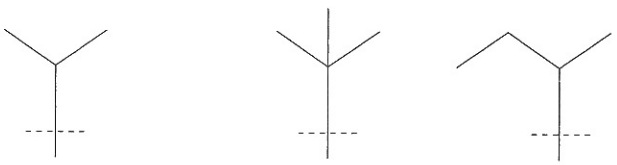


Figure 7-5: The common names of some substituents.

In the example shown in Figure 7-4, the substituent at carbon number four is, in fact, an isopropyl group. Now you have the name of the parent chain and the names of all of the substituents. The one-carbon substituent at carbon three is a methyl group, and the three-carbon substituent at carbon four is an isopropyl group. Now you just have to put it all together!

Ordering the substituents

The next step is to order the substituents alphabetically in front of the parent name, using numbers to indicate the location of the substituents. Since *i* comes before *m* in the alphabet, the *i*sopropyl group is placed in front of the *m*ethyl group in the name of the molecule: 4-isopropyl-3-methylheptane. Note that dashes are used to separate the numbers from the substituents, and that there is no space between the last substituent and the name of the parent chain.

Of course, there's always a stick to throw into the spokes. One quirk involving the common names of tert-butyl and sec-butyl substituents comes when placing them in alphabetical order, as the *tert* and *sec* portions of the name are ignored. In other words, tert-butyl would be ordered as if it started with the letter *b*, the same as with sec-butyl. Isopropyl, however, is alphabetized normally, under the letter *i*. (There always has to be weird exceptions like this, doesn't there?)

More than one-of-a-kind

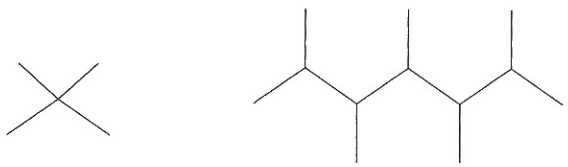
What if the molecule contains more than one of the same substituent? For example, what if the compound has two methyl group substituents on the molecule? In such a scenario, you don't name each of the methyl groups individually. Instead, you put a prefix in front of a single substituent name to indicate the number of these substituents that the molecule contains. (See Table 7-2 for a list of prefixes.)

Table 7-2 Prefixes for Identical Groups

Number of Identical Groups	*Prefix*
2	di
3	tri
4	tetra
5	penta
6	hexa

Number of Identical Groups	*Prefix*
7	hepta
8	octa
9	nona
10	deca

For example, if the molecule has two separate methyl groups, the prefix *di* goes in front of the name methyl, making the substituent name dimethyl. In addition, two numbers are placed in front of the substituent name to show the locations of the two methyl groups on the parent chain. If the molecule has three methyl groups coming off of the parent chain, the substituent name is trimethyl, if it has four methyls, the name is tetramethyl, if it has five methyls, the name is pentamethyl, and so on. These prefixes, like tert and sec in the previous examples, are ignored when placing the substituents in alphabetical order (dimethyl would be alphabetized under *m,* for example). For two examples of molecules that have identical substituents, see Figure 7-6. Note the use of commas to separate the numbers preceding the substituent name.



2,2-dimethylpropane 2,3,4,5,6-pentamethylheptane

Figure 7-6: Examples of multiple identical substituents.

Naming complex substituents

Sometimes, substituents will branch and will have no common name, like the substituent shown in Figure 7-7. In such a case, you name the substituent just as if it were a separate alkane, but with the parent name of the substituent ending with the suffix *yl* instead of *ane,* indicating that this portion of the molecule is a substituent off of the main chain.

The main catch in naming complex substituents, however, is that the carbon that attaches the substituent to the parent chain must be the number-one carbon; thus, when you number the carbons in the substituent chain, you force the carbon that attaches to the main chain to be carbon number one. (See Figure 7-8 for an example of how this works.)

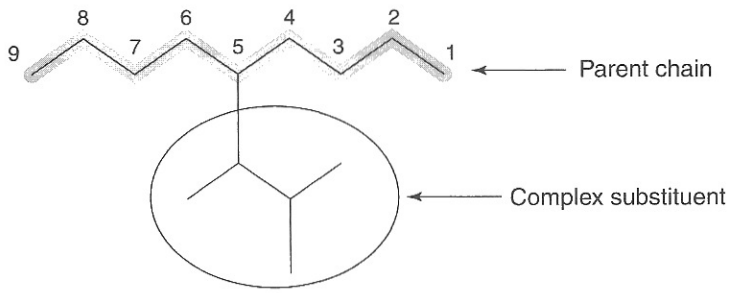


Figure 7-7: An alkane with a complex substituent.

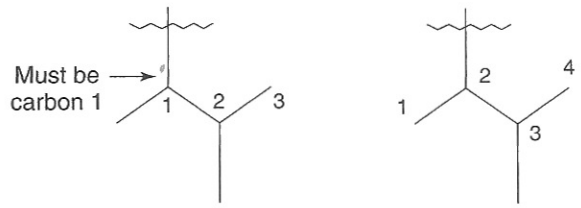


Figure 7-8: The right and wrong ways to number a complex substitutent.

Because the complex substituent shown in Figure 7-8 is three carbons long and has methyl groups at carbons one and three, the complex substituent is named 1,2-dimethylpropyl.



Because you're naming a substituent off of the parent chain, the name must end with the suffix *yl,* not *ane.*

Now you can put all of the parts of the name together. By convention, when a complex substituent is included in a name, the name of the complex substituent is set off with parentheses. So the name of the molecule in Figure 7-7 is 5-(1,2-dimethylpropyl)-nonane.

Getting lots of practice with naming alkanes is essential in order to master nomenclature of organic molecules.

Converting a Name to a Structure

It's just as important to be able to determine the structure from a name as it is to be able to determine the name of a structure. Although English reads from *left to right, the best way to read a structure's name is from right to left.* For example, if you want to draw the structure for 4-t-butyl-2,3,5-trimethylheptane,

you would start by first drawing the parent chain — heptane. Heptane is seven carbons long, so you draw a seven-carbon chain. See Figure 7-9.



Figure 7-9: The parent chain.

Then you number the carbon chain as shown in Figure 7-10.

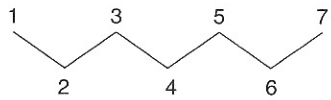


Figure 7-10: Numbering the chain.

Then you stick on the substituents. Substituents can be added in any order. A t-butyl group goes on the number-four carbon. (See Figure 7-11.)

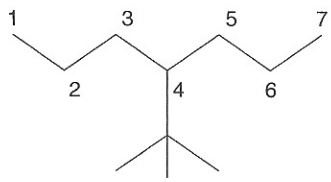


Figure 7-11: Adding a t-butyl group.

Then, methyl groups need to be plugged onto the carbons numbered two, three, and five, as shown in Figure 7-12.

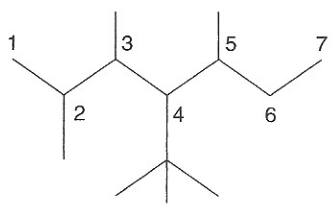
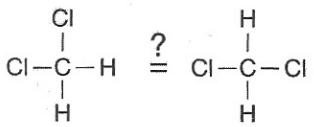


Figure 7-12: Adding methyls.

That's it! By reading the molecule from right to left, the structure is easily drawn from the name.

A word about drawing and interpreting structures

It is easy to become confused and misled by structures written on paper, because drawn structures are simply an organic chemist's way of conveniently representing a three-dimensional molecule on two-dimensional paper. For example, look at the following two structures and ask yourself if they refer to the same molecule or if they refer to different molecules.



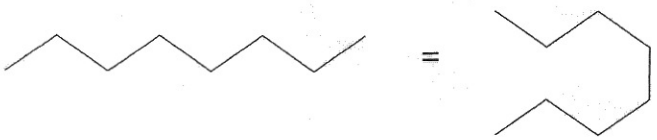
Are they the same or different?

Many people would say that they're different because they look different on paper. But both drawings are of the same molecule. The confusion results from the fact that a three-dimensional molecule is represented with a two-dimensional drawing. It looks on paper as if these molecules are flat and that each bond juts from the carbon at a 90° angle; in fact, the bonds are 109.5° apart from each other, and the molecule has a tetrahedral geometry (refer to Chapter 2).

Likewise, it is easy to get confused by drawings that look slightly different when they really represent the same thing. Whether you draw a straight chain with the first carbon up or the first carbon down is simply a matter of personal preference, because both represent the same molecule.



Additionally, don't get confused by molecules not drawn in a straight chain. Straight-chain molecules can be drawn in a straight line or in a snaking fashion.



The main point I want to make is that you should be mindful of the assumptions made in these structural drawings. I also want to encourage you to use molecular models (those plastic balls and sticks that represent atoms and bonds). Especially at the beginning of the course, molecular models come in handy, allowing you to get the feel of how two-dimensional drawings relate to the actual three-dimensional structures. After you get the feel of how the drawn structures relate to the molecular models, you'll be much less likely to become confused by the different ways that structures are drawn.

Problem Solving: Drawing Isomers from a Molecular Formula

Many times, at the beginning of organic chemistry, you're asked to draw out all the possible isomers given a molecular formula. These problems have a sneaky way of appearing on homework assignments and exams, and are of the kind in which you're asked to "draw as many of the structural isomers of the formula C_XH_Y as you can." These problems are useful because by working them you get a feel for the number of different molecules that are possible from a molecular formula. Additionally, these problems give you practice in naming alkanes.

Few textbooks give practical advice on how to solve such problems. So here's a systematic technique. In the following sections, I describe the technique and apply it to a problem to show you how to put the technique to practical use.

To describe the technique, I show you how to solve the following problem: "Draw all of the possible structures that have the formula C_6H_{14}." Here goes.

Step 1

First, you draw the main straight chain. You know from the formula C_6H_{14} that the structure represents a saturated alkane, because the formula follows the equation C_nH_{2n+2}. That means no double or triple bonds, or rings can be present in the molecule. Because you have six carbons in the formula, the main straight-chain molecule is hexane, with no branches. See Figure 7-13.



Figure 7-13: Hexane.

Step 2

Now you need to think about drawing the branched isomers. To do that, you draw the main chain minus one carbon. Because your main chain is six carbons long, you subtract one carbon to give five carbons (a pentane). You now

add a one-carbon unit (a methyl group) to the pentane to make as many isomers as you can, being careful not to duplicate structures (although if you do repeat structures they will caught in step 5). As a general rule, you don't want to add groups to the ends of the chains, because you'll end up duplicating a structure that you've already drawn. In the structure below (Figure 7-14), for example, don't add the methyl to the first or the fifth carbons. Doing so would duplicate the straight chain hexane isomer you've already drawn in step 1.

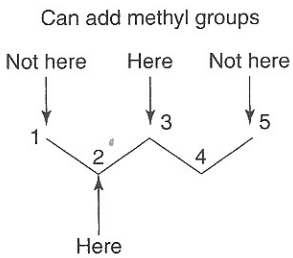


Figure 7-14: Adding methyls to pentane.

After you've drawn the five-carbon chain, look for the positions where the methyl group can be added. Because you don't want to add the methyl group to the ends of the chains, you can add the group to any of three spots — the second, third, and fourth carbons. However, if you draw one isomer with a methyl group at carbon number two, drawing another with the methyl at carbon number four would give the same exact molecule. (Name these two molecules and see that they have identical names, if you don't believe me.) You don't want to duplicate structures, so you should just draw one of them.



However, if you didn't recognize that two of the molecules are the same, and on an exam did draw the same structure twice, that's okay, because you have a check in step 5 to make sure that each of the structures you draw is unique.

The two unique structures that come from the molecule with a pentane parent chain are shown in Figure 7-15.

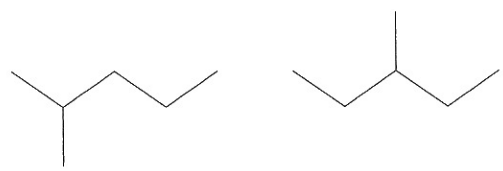


Figure 7-15: Pentane formulas.

Step 3

Now that you've drawn the isomers for the six- and the five-carbon chains, repeat the process with a four-carbon chain (a butane). With a four-carbon chain, you've subtracted two carbons from the parent chain, so you have to either add two one-carbon methyl groups, or add one two-carbon ethyl group.

Begin by drawing the four-carbon chain and thinking about where to add the two methyl groups. See Figure 7-16.

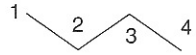


Figure 7-16: Butane.

You can add both methyl groups to the number two carbon (or both to the number three carbon, which will give the same molecule). Or, you can add one methyl to carbon number two and one to carbon number three. Again, you don't add to the end of the chains in order to avoid duplicating structures you've already drawn. This gives you two more isomers with the four carbon chain, shown in Figure 7-17.

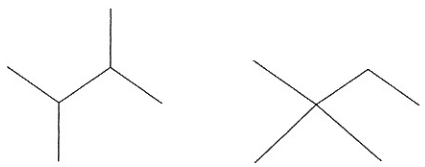


Figure 7-17: Butane isomers.

Step 4

You have now drawn out the six-, five-, and four-carbon chains. You could now try to go to the three-carbon chain, and then add three methyl groups, but in this case, doing so turns out to only repeat structures that you have already drawn, so I won't do so here. (This is not necessarily obvious; you should try this yourself.)

Step 5

Now you want to make sure that you didn't accidentally draw the same compound twice. To check for that, name each of the isomers (this is excellent practice at naming alkanes). If they all have different names, then they must be different; if two have the same names, then those two must be the same (even if they look different), and one should be discarded.

In this example, because all of the isomers drawn have different names, they're all different isomers of the formula C_6H_{14}. See Figure 7-18.

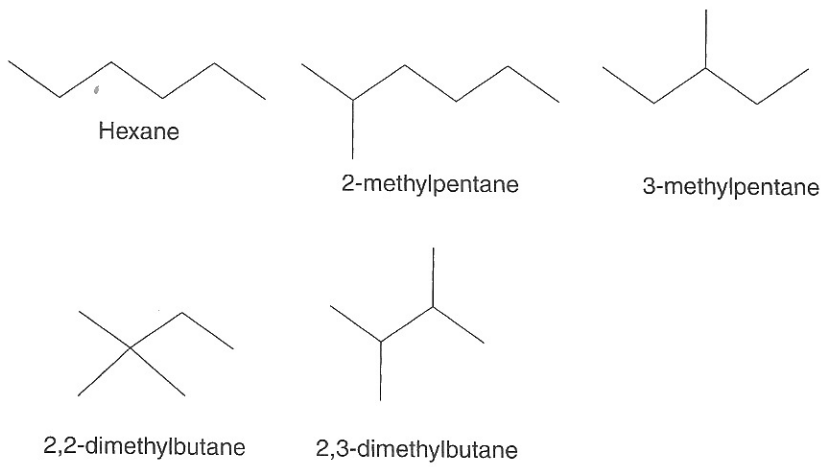


Figure 7-18: Naming the isomers.

Conformation of Straight-Chain Alkanes

Carbon-carbon single bonds are capable of rotating. This allows alkanes to exist in different *conformations*. What are conformations? Think of a molecule in terms of your body — you can flex it and bend it. You snuggle up in bed to read a book, you sit in class to hear a lecture, and you bend to do calisthenics to get your blood flowing in the morning. All of these activities put your body into different conformations. But these conformations are not of equal energy — lying down to read a book requires very little energy, sitting in class (and paying attention!) takes a bit more energy, and doing calisthenics requires a lot more energy. Now, which of these activities would you rather do? I'm guessing you'd rather be in the lower-energy conformation reading a book rather than in the high-energy conformation doing calisthenics.

Similarly, alkanes can exist in different conformations — different spatial arrangements of atoms — and not all the conformations are of equal energy. And molecules — like this author — prefer to be in low-energy conformations rather than high-energy conformations.

In the following sections, I talk about the different conformations of alkanes, how you can draw alkanes in different conformations using Newman projections, and how you can predict the relative energies of conformations.

Newman! Conformational analysis and Newman projections

One of the best ways to look at different conformations of molecules (individual conformations are called *conformers*) is to use Newman projections. A *Newman projection* is a convenient way of sighting down a particular carbon-carbon bond. Figure 7-19 shows a perspective drawing of ethane and the Newman projection of the same molecule. (See Chapter 6 for more on perspective drawings.)



The solid wedges in Lewis structures indicate a bond that's coming out of the paper, while dashed wedges indicate a bond that's going back into the paper.

In a Newman projection, the three lines in the shape of a Y represent the three bonds of the first carbon that you're sighting down; where the three lines connect is where the front carbon is. A circle (drawn "behind" the front carbon) represents the back carbon; the three lines coming out of the circle represent the three bonds that come off of that carbon. (Note that the fourth bond for each of these carbons is the carbon-carbon bond that you're looking down.) A Newman projection can help you analyze the rotations around a particular carbon-carbon bond.

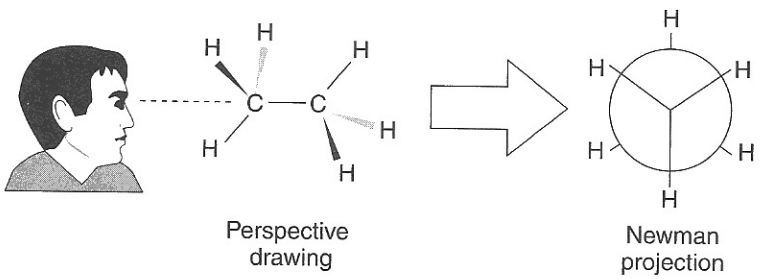


Figure 7-19: Making a Newman projection.



Using Newman projections, rotating around a specific bond to reach other conformers is a fairly straightforward task. The best way to reach other conformers is to rotate just one carbon at a time — either the front carbon or the back carbon. For consistency, in this book I will always hold the front of the Newman projection fixed and rotate the back carbon.

Although an infinite number of conformations exist (just rotate one of the carbons by a fraction of a degree and — *voila!* — you have a different conformation), the two most important ones are the eclipsed and staggered conformations (see Figure 7-20). An *eclipsed conformation* results when the bonds from the front carbon and the bonds from the back carbon align with each other, and the angle between the bonds (called the dihedral angle) is 0°. On the Newman projection, the eclipsed bonds are drawn a little ways apart so that the substituents on the back carbon can be seen. A *staggered conformation* results when the bonds from the front carbon and the bonds from the back carbon have a dihedral angle of 60°. In the staggered conformation, the bonds coming off of the front and back carbons are as far apart from each other as possible.

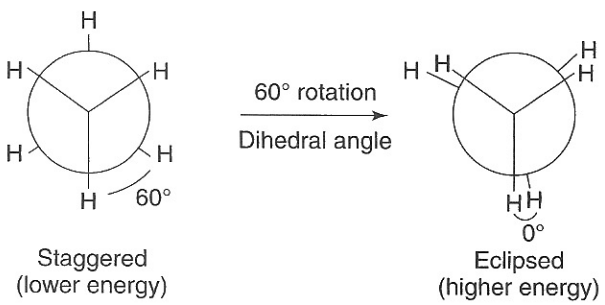


Figure 7-20: The staggered and eclipsed conformations in Newman projections.



When the bonds from the front carbon and back carbon are aligned in an eclipsed conformation, the electron repulsion between the bonds is higher than when the bonds are staggered and further apart. This electron-electron repulsion between the bonds is called *torsional strain.* Because staggered conformations have less torsional strain than eclipsed conformations, staggered conformations are, as a rule, more stable (that is, lower in energy) than eclipsed conformations.

Conformations of butane

The situation with butane is a bit more complicated than the situation with ethane. Figure 7-21 shows the Newman projection of butane, sighting down the bond between the second and third carbon (also known as the C2-C3 bond).

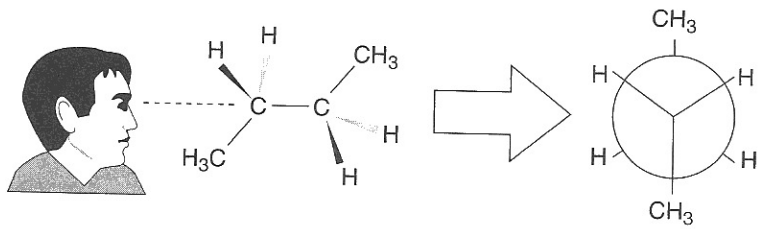


Figure 7-21: Sighting down the C2-C3 bond of butane.

With butane, not all eclipsed conformations are of the same energy, and not all staggered conformations are of the same energy. In Figure 7-22, I show the rotation around the C2-C3 bond in butane. In the first staggered conformation, the two methyl groups are 180° apart from each other. This conformer is called the *anti conformer.* In the other staggered conformer, the two methyl groups flank each other. The interaction between two adjacent large groups (like methyl groups) in a staggered conformation is called a *gauche interaction.* Gauche interactions act to increase the energy of a conformer. Because the staggered anti conformer has no gauche interactions, it's lower in energy than the staggered gauche conformer.

Generally, the following principle holds true: Big groups (like methyl groups) want to be as far away from each other as possible (so they don't invade each other's space), and conformers with the big groups far apart will be lower in energy than conformers where the big groups are near each other.

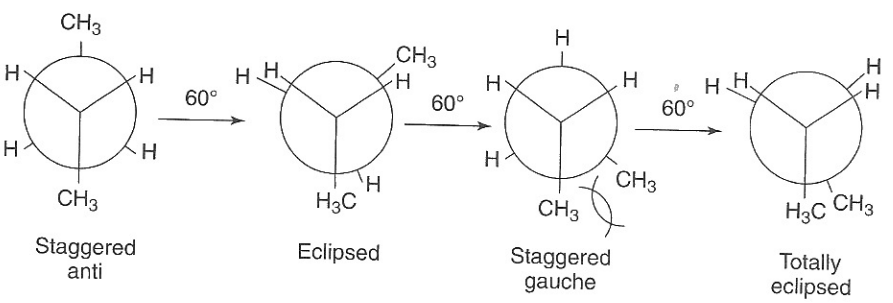


Figure 7-22: The conformations of butane formed by the rotation around the C2-C3 bond.

Likewise, the two eclipsed conformations are not of equal energy. In the first eclipsed conformation, the methyl groups are 120° apart; in the last eclipsed conformation, the methyl groups are 0° apart. This last conformer is called *totally eclipsed* to indicate that the two big groups are eclipsed with each other. Because the two big groups are closer together in the totally eclipsed conformer, this conformer is higher in energy than the other eclipsed

conformer. The energy diagram for converting the staggered anti into the totally eclipsed conformer is given in Figure 7-23, with the *x*-axis representing the rotation (in degrees) and the *y*-axis indicating the energy (in arbitrary units).

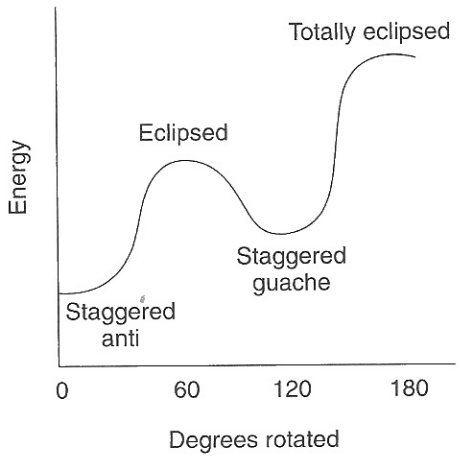


Figure 7-23: The energy diagram for butane conformers.

Full Circle: Cycloalkanes

Alkanes also commonly form into rings, called *cycloalkanes*. Cycloalkanes are named by counting the number of carbons in the ring, giving the same suffix as you would to a straight-chain alkane, and then giving the molecule the prefix *cyclo*. For example, a three-carbon ring is called cyclopropane. The smallest and most common rings are shown in Figure 7-24.

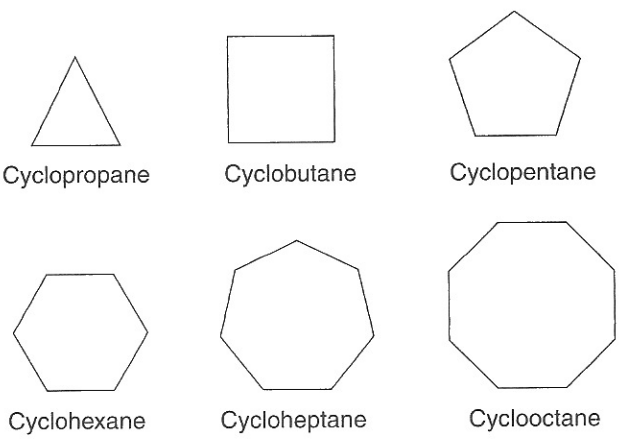


Figure 7-24: Common cyclic alkanes.

Stereochemistry of cycloalkanes

One interesting feature of cycloalkanes is that each ring has two distinct faces. If two substituents are attached to a cycloalkane ring, they can both point off of the same face, or they can point off of opposite faces of the ring. Consider 1,2-dimethylcyclopentane, shown in Figure 7-25 in both the traditional perspective view and in a slanted side view — called a *Haworth projection* — that's convenient for looking at the stereochemistry of rings. The two methyl groups could either point off of the same face (forming an isomer called a *cis stereoisomer*), or off of opposite faces (forming an isomer called a *trans stereoisomer*). *Stereoisomers* are molecules that have the same connectivity of atoms, but differ in the arrangement of those atoms in space.

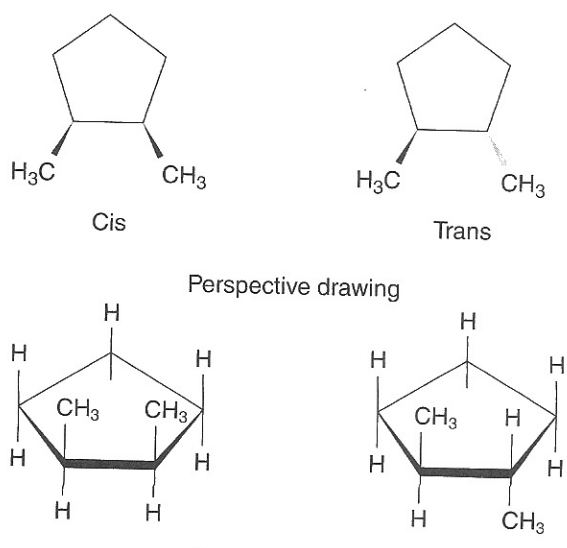


Figure 7-25: The cis and trans stereoisomers of 1,2-dimethylcyclopentane.

Conformations of cyclohexane

Although cyclohexane is typically drawn as if it were flat, in reality the structure is not flat at all. Most of the time, the structure exists in what is called the *chair conformation.* This conformation is called the chair because it looks (sort of) like a reclining lounge chair (see Figure 7-26). Other conformations for cyclohexane do exist — and they include the boat, half-chair, and twist-boat conformations — but the most important conformation is the chair because this conformation is typically the most stable conformation.

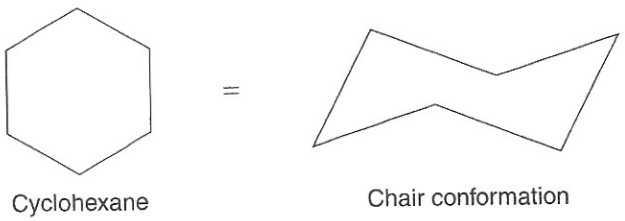


Figure 7-26: Chair conformation of cyclohexane.

Drawing chairs

Many find that drawing chairs can be somewhat difficult at first, but mastering the correct drawing of this conformation is essential for your success in orgo. To begin, start by drawing two lines that are parallel to each other but not perfectly horizontal, as shown in Figure 7-27. Next, add a downward-pointing V tip to one end (this is the *tail* of the chair). Finally, add an upward-pointing V tip to the other end (this is the *nose* of the chair).

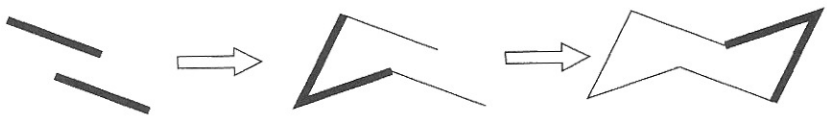
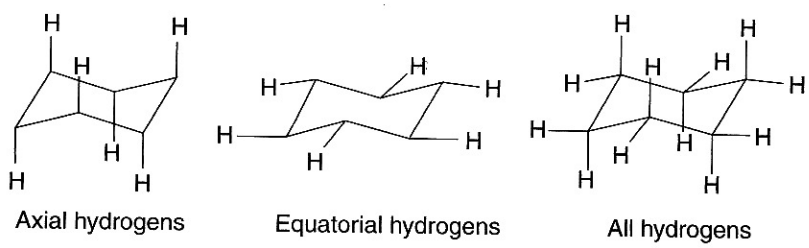


Figure 7-27: The steps involved in drawing the chair conformation of cyclohexane.

Adding hydrogens to a chair

A cyclohexane chair contains two kinds of hydrogens — axial hydrogens and equatorial hydrogens. *Axial hydrogens* are those hydrogens that stick straight up or straight down parallel to an imaginary axis through the chair; *equatorial hydrogens* are hydrogens that stick out along the equator of the chair (see Figure 7-28).

In drawing the hydrogens on a chair cyclohexane, it's often easiest to draw the axial hydrogens first. At any point on the chair that sticks up, put the axial hydrogen sticking straight up; at any point on the chair that sticks down, draw the axial hydrogen straight down. After the axial hydrogens are drawn, it's a fairly straightforward task to add in the equatorial hydrogens around the equator of the chair.



The axial and equatorial hydrogens on cyclohexane.

Flipping the chair

At room temperature, cyclohexane doesn't stay in one-chair conformation, but rapidly interconverts into an alternative chair conformation with a ring flip. A *ring flip* is shown in Figure 7-29. With the chair on the left of the figure, the nose of the cyclohexane chair goes down, and the tail of the cyclohexane goes up to make the new chair cyclohexane conformer. With a ring flip, all hydrogens that were originally axial become equatorial, and all hydrogens that were equatorial become axial. It's a good idea to get out your molecular models and try this ring flip yourself, so you can see it in three dimensions.

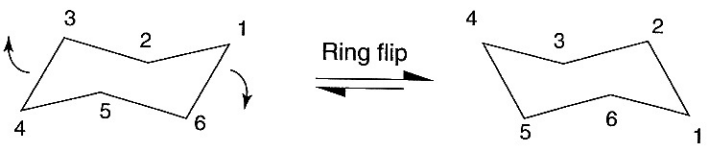


Figure 7-29: The ring flip of cyclohexane.

With unsubstituted cyclohexane (a cyclohexane that only has hydrogens attached to it), undergoing a ring flip doesn't change the molecule. With substituted cyclohexanes, however, the two chair conformers may not be identical. For example, isopropylcyclohexane is shown in Figure 7-30. One chair conformer puts the isopropyl group in the axial position. After undergoing a ring flip, the isopropyl becomes equatorial.



Ring flips change all axial positions to equatorial and all equatorial positions to axial.

These two conformers are not identical, and they don't have the same energy. When a large group is axial, the large group invades the space of the hydrogens on carbons three positions away, introducing *1,3-diaxial strain.* This interaction increases the energy of the axial conformer. Therefore, as a rule, large groups prefer to be equatorial because this conformation has no 1,3-diaxial strain (the right-pointing arrow is longer, indicating the direction of the equilibrium favors the more stable chair conformation). See Figure 7-30.

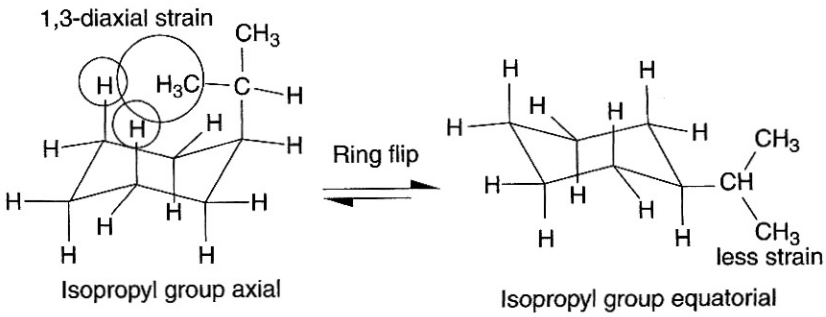


Figure 7-30: The chair conformers of isopropylcyclohexane.



Don't confuse conformation with configuration. A cis configuration (a molecule with substituents pointing off of the same face of the ring) or trans configuration (a molecule with substituents pointing off of opposite faces of the ring) doesn't change by changing the conformation. For example, a ring flip of a cyclohexane will not change a cis configuration to a trans configuration, because after the flip the substituents will still be pointing off of the same face (for a cis configuration) or off of opposite faces (for a trans configuration). The only way to change the configuration is by chemical reactions that make and break bonds.

Problem Solving: Drawing the Most Stable Chair Conformation

The first step in drawing the most stable conformation of cyclohexane is to determine — based on whether the substituents are cis or trans to one another, and based on where they're located on the ring — what the choices of axial and equatorial positions are for the substituents. A handy way of determining the substitution alternatives is to use the Haworth projection in Figure 7-31. This projection is easy to make — simply start at some position on the ring and alternate axial (a) and equatorial (e) from carbon to carbon, and from top to bottom. This projection will tell you what the two options for the two-chair conformations are.

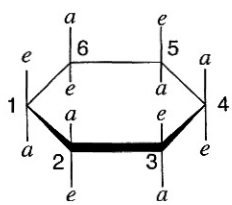


Figure 7-31: The Haworth projection.

For example, if you were asked to draw the most stable conformation of cis-1,3-dimethylcyclohexane, both substituents could either be on the top of the ring or both could be on the bottom of the ring as shown in Figure 7-32. (Recall that cis means that both substituents are on the same side of the ring.) As the figure shows, to get the cis stereochemistry, either both of the substituents could be equatorial (both e), or both could be axial (both a).

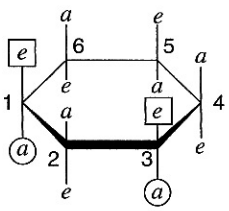


Figure 7-32: The possible positions of cis substituents in positions 1 and 3 on cyclohexane.



It is energetically favorable to put large groups in the equatorial position to eliminate 1,3-diaxial strain.

Because large groups prefer to be equatorial, the most stable conformer for cis-1,3-dimethylcyclohexane is the diequatorial conformer, shown in Figure 7-33. The diaxial conformer would be higher in energy.

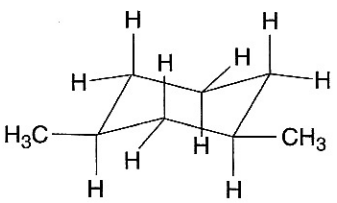


Figure 7-33: The diequatorial conformation of cis-1,3-dimethylcyclohexane.



If cyclohexane has two substituents and one has to be placed axial and one equatorial (as is the case in trans-1,2-disubstituted cyclohexanes), the lowest energy conformation will be the one in which the bigger group goes in the equatorial position and the smaller group goes in the axial position.

Reacting Alkanes: Free Radical Halogenation

Because alkanes are essentially inert under most conditions, virtually the only reaction of alkanes that you see is the free-radical halogenation reaction. This reaction is often the first reaction that you encounter in organic chemistry. Occasionally, textbooks discuss the *catalytic cracking reaction* of large alkanes — the heating of long-chain fossil fuel alkanes over a catalyst — a process that breaks large alkanes into smaller fragments. But that reaction is a large-scale commercial process used in industry to make gasoline, and isn't a reaction that's useful in a typical laboratory.

The chlorination of methane is shown in Figure 7-34. In this reaction, a chlorine atom is substituted for a methane hydrogen.

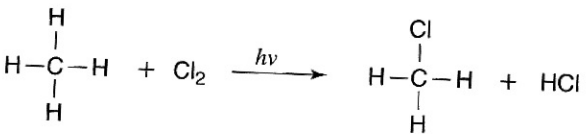


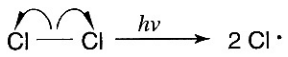
Figure 7-34: The chlorination of methane.

One feature that's interesting about this chlorination reaction is that the reaction is *photochemical:* Instead of using heat to start the reaction, the reaction uses light (abbreviated $h\nu$)! The reaction proceeds in three stages — initiation, propagation, and termination.

Getting things started: Initiation

In the initiation step, light is shone on the reaction and absorbed by the chlorine (Cl_2). The light provides enough energy for the married chlorines to divorce — that is, for the chlorine-chlorine bond to break apart to form two chloride radicals, as shown in Figure 7-35. (Recall that free radicals are compounds that contain unpaired electrons.) This kind of bond dissociation is called *homolytic cleavage,* because the bond breaks symmetrically — one electron from the bond goes to one side, and the other electron goes to the other side, just as half of the shared property goes to each person in a divorce (theoretically). Note that you use one-headed fishhook arrows to show the movement of only one electron. See Chapter 3 for more on using arrows in organic chemistry.

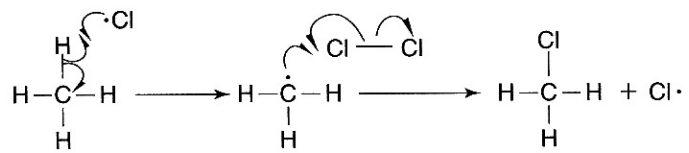
Figure 7-35: The initiation step.



Keeping the reaction going: Propagation

After the reaction has been initiated by forming the chloride radicals, the reaction proceeds to the propagation steps (see Figure 7-36). A chloride radical is unstable because the chlorine atom only has seven valence electrons, one electron short having its valence octet completely full. To fill its valence octet, a chloride radical then plucks a hydrogen atom (not a proton) from the methane to make hydrochloric acid plus the methyl radical. Now, however, the methyl radical is one electron short of completing its octet. So, the methyl radical then attacks another molecule of chlorine to make chloromethane plus another chloride radical.

Figure 7-36: The propagation steps.



You're fired: Termination steps

Because this reaction generates chloride radicals as a byproduct, the reaction is called a chain reaction. In a *chain reaction,* the reactive species (in this case, the chloride radical) is regenerated by the reaction. If not for the termination steps, this reaction could theoretically continue until all of the starting materials were consumed. Termination steps are reactions that remove the reactive species without generating new ones. Any of the radical couplings shown in Figure 7-37 are considered termination steps because they remove the reactive species (the free radicals) from the reaction without replacing them.



When solving multistep synthesis problems (see Appendix A), you're often given an alkane-starting material. One of the best ways to get your foot in the door (often the only way) as far as putting a functional group on the molecule is to brominate (or chlorinate) the alkane using this free-radical reaction.

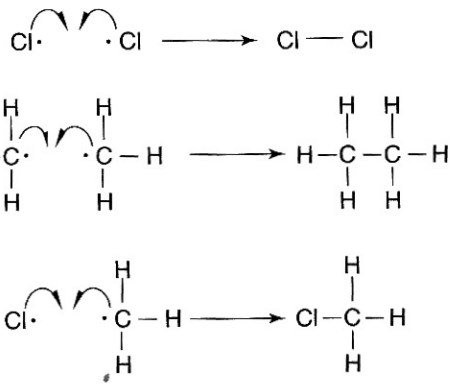


Figure 7-37: The termination steps for the chlorination of methane.

What about the chlorination of larger molecules that have different kinds of hydrogens? While in methane only one kind of hydrogen is available to be pulled off — and so only one possible product can be made — in larger molecules several products can be formed. For example, butane (Figure 7-38) has two types of hydrogen. Hydrogens are classified according to the substitution of the carbon to which they're attached. Hydrogens attached to primary carbons (or carbons bonded to only one other carbon) are called primary hydrogens, hydrogens attached to secondary carbons (or carbons bonded to two other carbons) are called secondary hydrogens, and so on. Butane has two types of hydrogens — primary hydrogens (1°) and secondary hydrogens (2°).

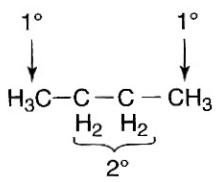


Figure 7-38: The primary and secondary hydrogens on butane.

The chlorination of butane selectively forms the product that results from the chloride radical abstracting a secondary hydrogen to make the secondary radical, as shown in Figure 7-39.

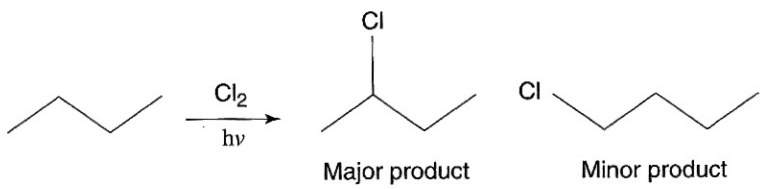
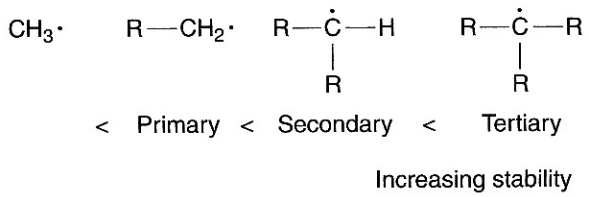


Figure 7-39: The chlorination of butane.

To see why this is so, you need to consider the stabilities of free radicals. Radicals are more stable when they rest on more highly substituted carbons, as Figure 7-40 shows. Thus, you preferentially get chloride substitution on the more highly substituted carbon atom.



Selectivity of chlorination and bromination

The bromination of alkanes occurs in the same fashion as the chlorination of alkanes, except that Br_2 is used in the reaction instead of Cl_2. One difference between the chlorination and bromination of alkanes is that bromide radicals are more selective for hydrogen on more substituted carbons than chloride radicals.

What do I mean by selectivity? Consider the politically incorrect analogy of the selectivity of a mass murderer versus the selectivity of a wife who just found out her husband had been cheating on her. A mass murderer has little selectivity — he kills virtually everyone he meets. The angry wife, however, is much more selective: She may bump *into* many people, but she only bumps *off* her husband. In a similar way, bromide radicals are more selective than chloride radicals. A chloride radical is like the mass murderer, and a bromide radical is like the angry wife. Chloride radicals have only modest selectivity for choosing hydrogens on more substituted carbons, reacting many times with any hydrogen it bumps into. Bromide radicals, however, more selectively choose to react with hydrogens on the more highly substituted carbons.

Chapter 8

Seeing Double: The Alkenes

- Defining alkene stereochemistry
- Adding alkene nomenclature to your repertoire
- Seeing the reactions of alkenes

At this point, I assume you know the basics of organic chemistry. I assume you understand the difference between covalent and ionic bonds (Chapter 2), how to draw and interpret organic structures (Chapter 3), and how to name alkanes (Chapter 7). In construction terms, I assume you have the foundations of the house of organic chemistry. Now that the foundation is there, I get to the fun stuff — the chemical reactions, themselves — which build up the walls of the house of organic chemistry (that Jack built).

Specific chemical reactions are the meat and potatoes of most organic chemistry courses. And as the number of reactions that you see start to pile up like dirty socks on the floors of college dormitories, organizing all of the many reactions in as succinct and as convenient a way as possible becomes essential. With the alkene functional group, numerous reactions are available to both form alkenes and convert them into other functional groups.

In this chapter, I introduce the alkene functional group. I show you how to add the nomenclature of alkenes into your repertoire, and I discuss the many reactions that both make alkenes and transform them into new kinds of compounds. Along the way, I give you practical advice on how you can best learn the swarms of reactions that you will see throughout this chapter and in your organic course.

Defining Alkenes

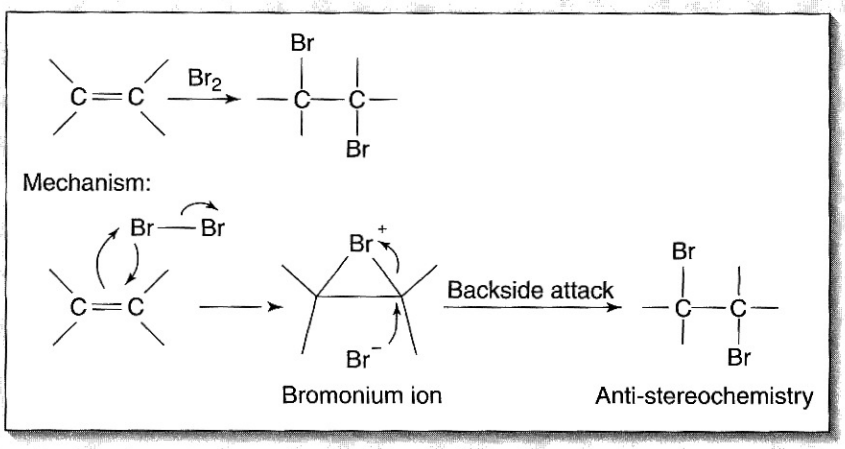
Alkenes are compounds that contain carbon-carbon double bonds. Because alkenes are so often found in valuable compounds (like pharmaceuticals), they're one of the most important functional groups in organic chemistry. Alkenes are also very versatile, as they are easy to make and convert into other molecules, as Figure 8-1 shows. Therefore, alkenes become useful as waypoints on the road to synthesizing other molecules.

Mastering organic reactions

Many students find that making reaction note cards (like the one shown in the accompanying figure) is a helpful way to learn the reactions (I highly recommend this practice). Others find that reaction schemes that organize functional group conversions visually (like the one shown in Figure 8-1) are very helpful for learning the reactions.

No matter how you choose to learn the reactions, you should work many problems that test your ability to recall reactions and apply these reactions to new situations. Because most of organic chemistry involves reactions of organic molecules, you need to become an "expert" in synthetic organic chemistry. And to become an expert at anything you need to practice. To become an expert pianist, you need to practice the piano; to become an expert painter, you need to practice painting; and to become an expert whistler, you need to practice whistling. In the same way, to become an expert in organic reactions, you need to practice, practice, practice.

In a practical sense, you should work many problems that test both your ability to recall the reactions (including which reagents to use), and your ability to apply what you know to new circumstances. At first, you'll just deal with one-step reactions — what reagents convert Compound A into Compound B, for example. But eventually you'll need to be able to work multistep synthesis problems, that is, syntheses involving more than one step, which I discuss in more detail in Appendix A.



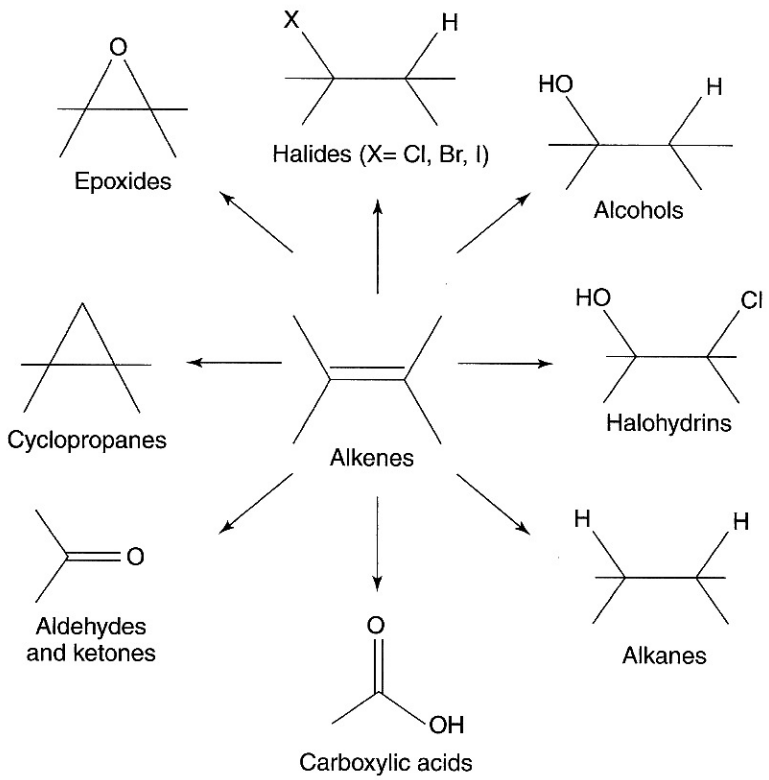


Figure 8-1: Some of the compounds that can be made from alkenes.

What do I mean by *waypoints?* Think of air travel as an analogy. You might not be able to get a flight directly from Florida to Timbuktu, but you might be able to get a thruway flight from Florida to Georgia, and from Georgia you could get a flight to Timbuktu. Similarly, you might not be able to convert one functional group directly into the functional group that you want, but you might be able to convert the functional group into a thruway functional group (like an alkene), which could then be converted into the desired product. So, even if a desired product contains no carbon-carbon double bonds, alkenes may still play a role in the synthesis of that molecule.

Taking Away Hydrogens: Degrees of Unsaturation

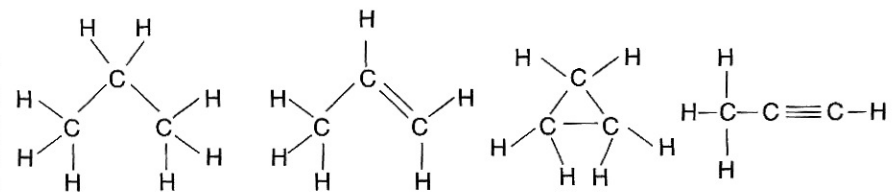
Alkanes are said to be saturated hydrocarbons because these molecules are saturated with hydrogens, holding the maximum number of hydrogens while still obeying all of the rules of valence (having no more than four bonds for

second-row atoms). Because adding a carbon-carbon double bond in a molecule requires the loss of two hydrogens, alkenes are said to add a *degree of unsaturation* into a molecule (sometimes called a *double bond equivalent* or *index of hydrogen deficiency*). So, while alkanes have the general formula C_nH_{2n+2}, where n is the number of carbon atoms in the molecule, alkenes have the general formula of C_nH_{2n} and contain two fewer hydrogens than an alkane with the same number of carbons.

Determining degrees of unsaturation from a structure

Knowing the number of degrees of unsaturation in a molecule is useful because this number gives you an indication of how many double bonds are present in an unknown compound. (This morsel of information becomes very useful when you want to determine the structure of an unknown compound. See Part IV for how to apply this information to spectroscopy and spectrometry problems.)

The degrees of unsaturation in a molecule are additive — a molecule with one double bond has one degree of unsaturation, a molecule with two double bonds has two degrees of unsaturation, and so forth. Just as the formation of a double bond causes two hydrogens to be lost, the formation of a ring also results in the loss of two hydrogens, so every ring in the molecule also adds one additional degree of unsaturation. For every triple bond, two degrees of unsaturation are added to a molecule, because a molecule must lose four hydrogens to make a triple bond. Some examples of three-carbon molecules with different numbers of degrees of unsaturation are shown in Figure 8-2.



C_3H_8
Hydrogen saturated

C_3H_6
1 degree of unsaturation

C_3H_6
1 degree of unsaturation

C_3H_4
2 degrees of unsaturation

Figure 8-2: The degrees of unsaturation for three-carbon molecules.

To determine the number of degrees of unsaturation for any arbitrary structure, you sum all the individual elements of unsaturation in the molecule.

Figure 8-3 shows a molecule that consists of one ring, one double bond, and one triple bond. This molecule, therefore, has four degrees of unsaturation because the double bond and the ring each adds one degree of unsaturation, and the triple bond adds two degrees, for a total of four.

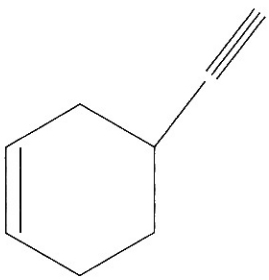


Figure 8-3: A molecule with four degrees of unsaturation.

Problem solving: Determining degrees of unsaturation from a molecular formula

More important than determining the number of degrees of unsaturation from a molecular structure is being able to determine the number of degrees of unsaturation from a molecular formula. The number of degrees of unsaturation can be determined from the molecular formula using the following equation.

$$\text{degrees of saturation} = \frac{\left[(\text{number of carbons} \times 2) + 2\right] - \text{number of hydrogens}}{2}$$

With this equation, the number of degrees of unsaturation can be determined for any hydrocarbon whose molecular formula is known. (For compounds whose structure and formula are not known, chemists use an instrumental technique called mass spectrometry to determine the molecular formula of the compound. See Chapter 14 for more on mass spec.) But what about molecules that contain atoms other than hydrogen and carbon? In such cases, you need to convert these multi-atom molecular formulas into equivalent formulas that contain just carbon and hydrogen so they can be plugged into the above equation. To do so, you use the following conversion factors.

- **Halogens (F, Cl, Br, I):** Add one hydrogen to the molecular formula for each halogen present
- **Nitrogen:** Subtract one hydrogen for each nitrogen present
- **Oxygen or sulfur:** Ignore

For example, to determine the number of degrees of unsaturation in the formula $C_8H_6F_3NO_2$, you first make the proper substitutions for all atoms that are not hydrogen and carbon. Fluorine is a halogen, so you add three hydrogen atoms to the molecular formula (one for each F). The molecule contains one nitrogen, so you subtract one hydrogen from the molecular formula. The two oxygens in the molecule you ignore. This gives a reduced equation of $C_8H_{6+3-1} = C_8H_8$. In other words, both the formula $C_8H_6F_3NO_2$ and the formula C_8H_8 have identical numbers of degrees of unsaturation. Plugging this reduced formula into the above equation gives five degrees of unsaturation for the molecular formula $C_8H_6F_3NO_2$.

Nomenclature of alkenes

If you know how to name alkanes (see Chapter 7), adding alkene nomenclature to your repertoire is a fairly straightforward task. While the names of alkanes end with the suffix *-ane*, alkenes end with the suffix *-ene*. A two-carbon alkene, therefore, is named ethene; a three-carbon alkene is named propene, and an alkene in a five-membered ring is named cyclopentene see Figure 8-4.

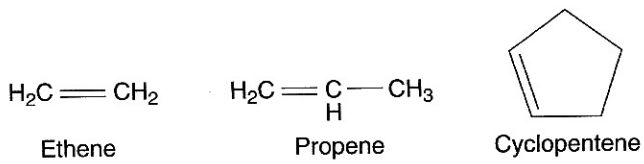


Figure 8-4: The structures of some alkenes.

Numbering the parent chain

For molecules in which the double bond can be put in more than one position, you must put a number in front of the parent name to indicate the position of the double bond. For example, two alkene locations in pentene are possible (see Figure 8-5), so a number must be placed in front of the name to show the location of the double bond.



Figure 8-5: The two possible locations.

The parent chain is numbered so that the alkene is given the lowest possible number. For example, you wouldn't name the pentene 3-pentene because that would be an identical structure to 2-pentene. Figure 8-6 shows the correct and incorrect numbering in a seven-carbon chain with a methyl substituent. Notice that giving the smaller number to the double bond takes precedence over assigning the smaller number to the substituent.

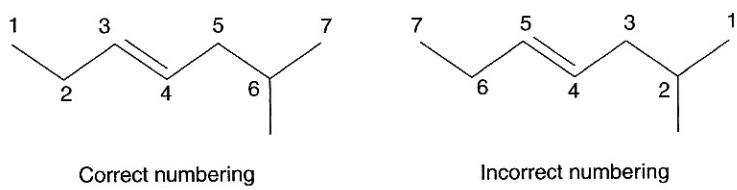


Figure 8-6: The correct and incorrect numberings of a long-chain alkene.

Additionally, the alkene *must* be included in the parent chain, even if a longer chain of carbon atoms can be found that doesn't include the alkene. Figure 8-7 shows how this works.

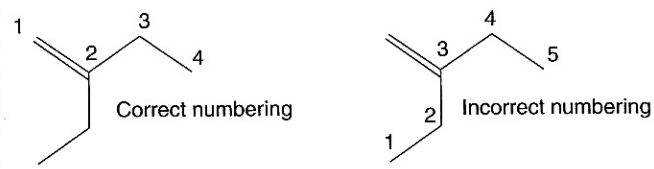


Figure 8-7: The correct and incorrect numberings of an alkene.

To number an alkene in a ring, number around the ring so that the double bond has the lowest possible number, as shown in Figure 8-8.

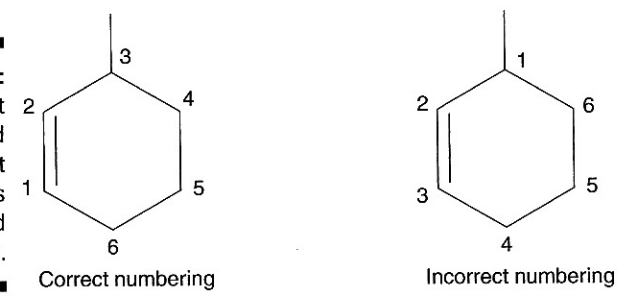
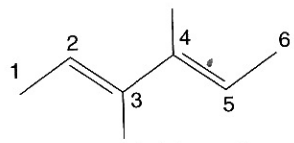


Figure 8-8: The correct and incorrect numberings of a ringed alkene.

Adding multiple double bonds

The naming of alkenes with more than one double bond requires the use of a prefix (such as *di, tri, tetra,* and so forth) to indicate the number of double bonds in the molecule. Also, the position of all double bonds is indicated with numbers at the beginning of the name. An example of how this is done is shown in Figure 8-9.

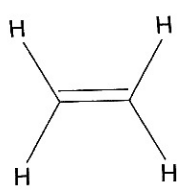


3,4-dimethyl-2,4-hexa*di*ene

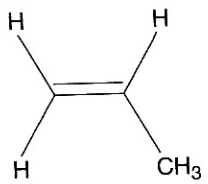
Figure 8-9: The numbering and naming of a dialkene containing two methyl substituents.

Common names of alkenes

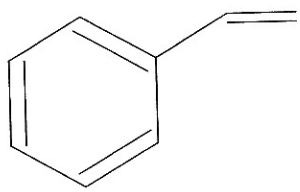
While alkenes can be named systematically using the IUPAC nomenclature (the *IUPAC nomenclature* is the official nomenclature system of chemists) as outlined above, some alkenes have common names that come from the olden days. These older names (some of which are shown in Figure 8-10) are still often seen in the literature and need to be memorized. For some smaller alkenes, the suffix *-ylene* is used instead of simply *-ene.* Ethene, for example, is usually called ethylene, and propene is called propylene. Styrene — the compound used to make the plastic polystyrene — is the common name for a molecule that consists of a double bond jutting off of a benzene ring (see Chapter 13 for a discussion of benzene and other ringed compounds).



Ethylene



Propylene



Styrene

Figure 8-10: The common names of some alkenes.

Stereochemistry of alkenes

Unlike carbon-carbon single bonds, which are free to rotate (see Chapter 7), double bonds are fixed and rigid. In other words, rotation around carbon-carbon double bonds is not possible at reasonable temperatures. Therefore, molecules containing double bonds have the possibility of having stereoisomers, just as ring systems do.

Molecules that have the same connectivity of atoms, but different orientations of those atoms in space are called stereoisomers (see Chapter 7).

Same side or opposite sides? Cis and trans stereochemistry

Consider the case of 2-pentene, shown in Figure 8-11. In this alkene, two stereoisomers are possible. One stereoisomer, called the *cis* stereoisomer, has both of the double-bond hydrogens on the same side of the double bond, while the other stereoisomer, called the *trans* stereoisomer, has the two hydrogens on opposite sides of the double bond. In general, when two identical groups are on the same side of the double bond, the molecule is said to possess *cis* stereochemistry; when two identical groups are on opposite sides of the double bond, the molecule is said to possess trans stereochemistry.

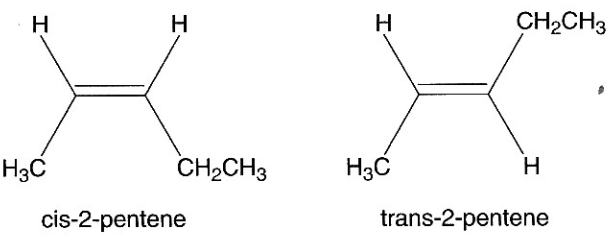


Figure 8-11: Cis and trans 2-pentene.



You can only have cis-trans stereochemistry in rings and on double bonds. You cannot have cis-trans isomers on single bonds due to the rapid free rotation of these bonds at room temperature. (Take a peek at the section on Newman projections and conformations in Chapter 7.)

Playing a game of high-low: E/Z stereochemistry

What if a double bond holds four nonidentical groups? In such a case, the cis-trans nomenclature doesn't apply because cis-trans nomenclature can only be used when two *identical* groups are attached to a double bond or ring (in many cases, these identical groups are simply hydrogens). When four non-identical groups are attached to a double bond, you must use the E/Z system of nomenclature (rather than the cis-trans nomenclature) to assign the stereochemistry of the double bond. (E stands for the German word *entgegen,* which means "opposite," while Z stands for the German word *zusammen,* which means "together.")

To use the E/Z system of nomenclature, you have to play a game of high-low. First, you must decide which substituent is given higher priority and which is given lower priority using the Cahn-Ingold-Prelog prioritizing scheme on both sides of the alkene. Figure 8-12 helps you visualize this process

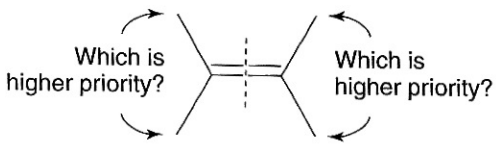


Figure 8-12: Assigning E/Z stereochemistry.

If the two high-priority substituents are on the same side of the double bond, the alkene is given the Z nomenclature; if the highs are on opposite sides of the double bond, the alkene is given the E nomenclature. See Figure 8-13 for an illustration of these nomenclature rules.

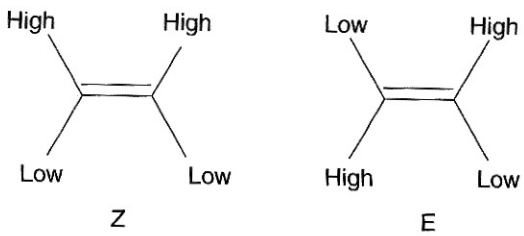


Figure 8-13: Playing high-low.

Here's how to prioritize the double-bond substituents using the Cahn-Ingold-Prelog prioritizing scheme.

- **Individual substituents:** The substituent whose first atom has the highest atomic number gets the highest priority. For example, iodine would be higher priority than bromine, which would be higher than fluorine.
- **Ties:** In the case of a tie (both first atoms are carbon, for example), proceed to the next atom and decide which atom has the higher atomic number. If you get another tie, keep going until the tie is broken. (See Figure 8-14 for an example.)
- **Multiple bonds:** You treat multiple bonds in a somewhat strange fashion using the Cahn-Ingold-Prelog prioritizing scheme. Using this prioritizing scheme, you treat multiple bonds as if they were multiple single bonds. A carbon double-bonded to oxygen, for example, would be treated as if the carbon had two carbon-oxygen single bonds (and as if each oxygen were bonded back to carbon). Which is higher priority, the carbon double-bonded to oxygen or the carbon triple bonded to nitrogen as shown in Figure 8-15? The carbon double-bonded to oxygen is higher priority because oxygen has a higher atomic number than nitrogen. (The fact that one molecule has three C-N bonds and the other has only two C-O bonds is irrelevant; the number of bonds only matters when comparing identical bonds, so C=NH would be higher priority than C-NH_2.)

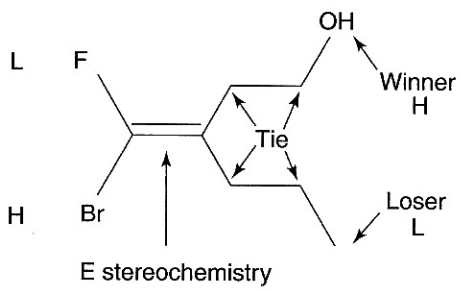


Figure 8-14: Determining the priorities of double-bond substituents in cases of ties.

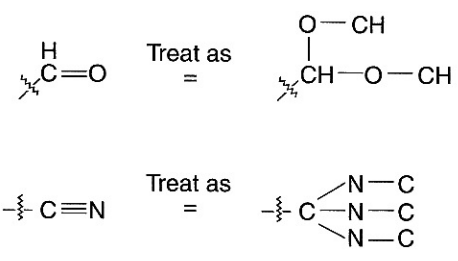


Figure 8-15: Treating multiple bonds using the Cahn-Ingold-Prelog prioritizing scheme.

Stabilities of Alkenes

Reactions yielding alkenes often preferentially form certain alkene isomers over others. In many cases, this preference for one isomer over another is the result of one isomer being more stable than another, with the more stable isomer being formed preferentially. Understanding what structural features lead to this greater alkene stability helps you to justify why certain alkenes will be formed in particular reactions.

Alkene substitution

Perhaps the biggest factor affecting the stability of alkenes is the number of non-hydrogen substituents that come off of the carbon-carbon double bond. In general, the more non-hydrogen substituents that come off a double bond, the more stable the alkene is, as shown in Figure 8-16.

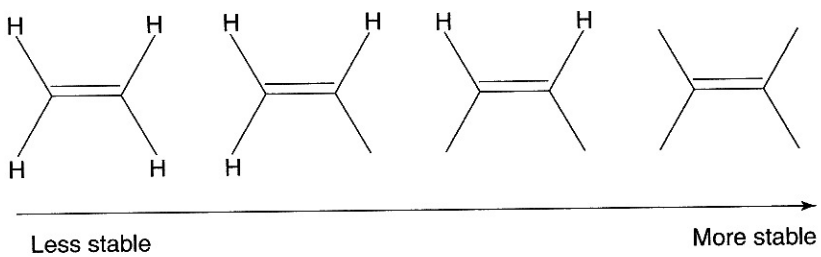


Figure 8-16: The relative stabilities of substituted alkenes.

Stability of cis and trans isomers

Also affecting the stability of alkenes is cis-trans isomerism. Generally, trans isomers of alkenes are more stable than cis isomers. This preference of alkenes for trans isomers comes about because atoms (like people) want a certain amount of personal space, and atoms don't like to have their personal space invaded. Technically, this desire for adequate space results from atoms repelling each other because of the electron-electron repulsion of their electron clouds.

Alkenes in the trans configuration have substituents that are on opposite sides of the double bond, and the bulky substituents are thus farther away from each other; alkenes in the cis configuration, on the other hand, have substituents that are on the same side of the double bond, and the substituents are close to each other, invading each other's space. The electron-electron repulsion that

results from atoms being forced into the personal space of other atoms is called *steric repulsion,* as shown in Figure 8-17. Therefore, alkenes prefer to be in trans configuration rather than cis configuration.

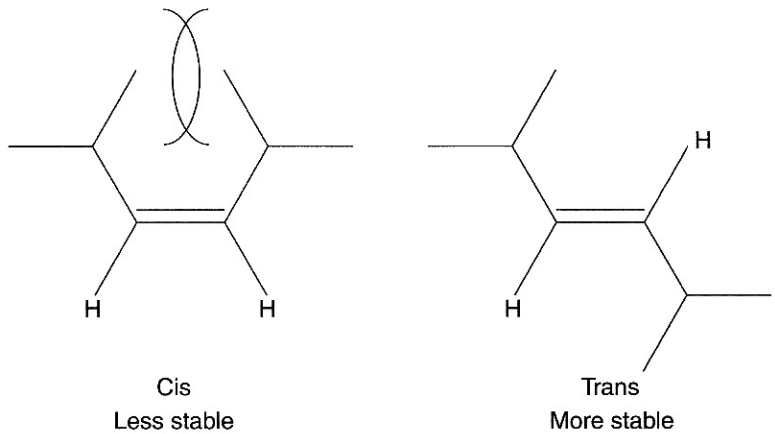


Figure 8-17: The steric repulsion of cis alkenes and the relative stabilities of cis and trans alkenes.



To say that one molecule is more stable than another is generally synonymous with saying that one is lower in energy than another. In other words, stable molecules are generally lower in energy than unstable molecules.

Formation of Alkenes

The three primary ways to form alkenes is by dehydrohalogenation, dehydration, and the Wittig reaction.

Elimination of acid: Dehydrohalogenation

One of the most common methods of making alkenes is from alkyl halides. Halogens are often abbreviated X, which stands for any of the halogens chlorine (Cl), bromine (Br), or iodine (I). When a strong base (abbreviated $B:^-$) is added to an alkyl halide, one equivalent of a hydrohalic acid (HX) is eliminated from the molecule to make the alkene. This process is called *dehydrohalogenation,* and is shown in Figure 8-18. The proton that's eliminated is a proton adjacent to the halide, not a proton on the same carbon as the halide. The two possible mechanisms for this elimination are discussed in detail in Chapter 10.

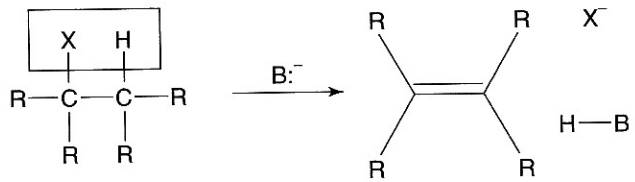


Figure 8-18: The dehydrohalogenation of an alkyl halide.

Losing water: Dehydration of alcohols

Similar to the process of dehydrohalogenation of alkyl halides is the process of *dehydration,* or the loss of water to make alkenes. In the presence of a strong acid and heat (abbreviated Δ), alcohols lose water to make alkenes, as shown in Figure 8-19. These dehydration reactions typically follow the E1 mechanism discussed in Chapter 10.

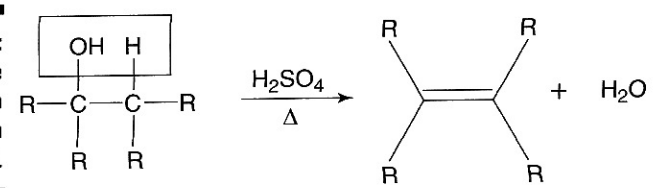


Figure 8-19: The dehydration of an alcohol.

Alkenes from coupling: The Wittig reaction

A very useful reaction for making alkenes is the Wittig reaction (pronounced "*Vittig*"), a reaction for which Georg Wittig, the chemist who discovered it, received the Nobel Prize in chemistry.



If you want to win a Nobel Prize in chemistry, a good way to start is to discover a general carbon-carbon bond-making reaction, because such reactions are extremely valuable. Chemists who have won Nobel Prizes for doing just that include Otto Diels, Kurt Alder, Georg Wittig, and Victor Grignard.

In the Wittig reaction, an aldehyde or ketone is reacted with a phosphorane (phosphorous double bonded to carbon, $Ph_3P{=}CR_2$) to make an alkene, as shown in Figure 8-20. (Remember that Ph stands for a phenyl ring, C_6H_5.) From a conceptual standpoint, you can imagine snipping off the carbonyl

oxygen and the triphenylphosphine (PPh_3) portion of the phosphorane, and then smooshing the two parts together to make the alkene.

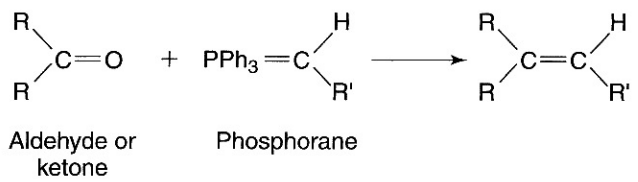


Figure 8-20: The Wittig reaction.

Making a phosphorane requires two steps. First, triphenylphosphine (Ph_3P) is reacted with a primary alkyl halide to make a phosphonium ion, as shown in Figure 8-21. Then, a strong base ($B:^-$) is added to deprotonate the carbon adjacent to the phosphorous, making the phosphorane; this phosphorane has two major resonance structures.

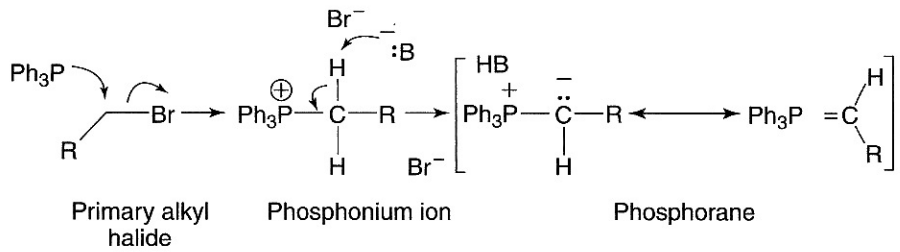


Figure 8-21: Making phosphorane.

The mechanism of the addition of the phosphorane to the carbonyl compound (usually an aldehyde or ketone) is still disputed, but chemists think that the attack of the phosphorane on the carbonyl compound generates a charged species called a *betaine,* as shown in Figure 8-22. The *oxyanion* (negatively charged oxygen) of the betaine then attacks the positively charged phosphorous to generate a four-membered neutral species called an *oxaphosphetane.* The oxaphosphetane collapses to generate a very stable triphenylphosphine oxide and the alkene. (Whew!)

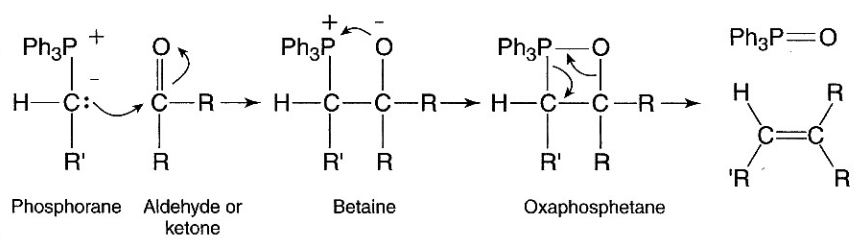


Figure 8-22: The mechanism of the Wittig reaction.

Reactions of Alkenes

One of the most useful aspects of alkenes is that they can be made into such a variety of different compounds.

Adding hydrohalic acids across double bonds

Adding a hydrohalic acid (usually HCl or HBr) to a double bond converts the alkene into an alkyl halide. This reaction, shown in Figure 8-23, is just the reverse reaction of the elimination reaction that creates double bonds.

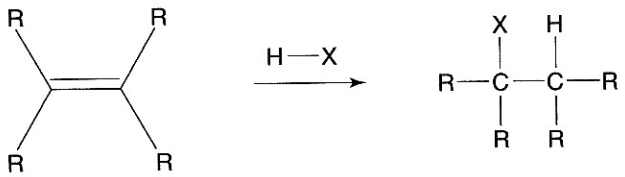


Figure 8-23: Markovnikov addition to alkenes.

The mechanism of the reaction is shown in Figure 8-24. The first step of the reaction is protonation of the double bond by the acid. This leads to a short-lived *carbocation* intermediate (cations on carbon atoms are called carbocations). The carbocation is then attacked by the free halide anion to generate the alkyl halide.

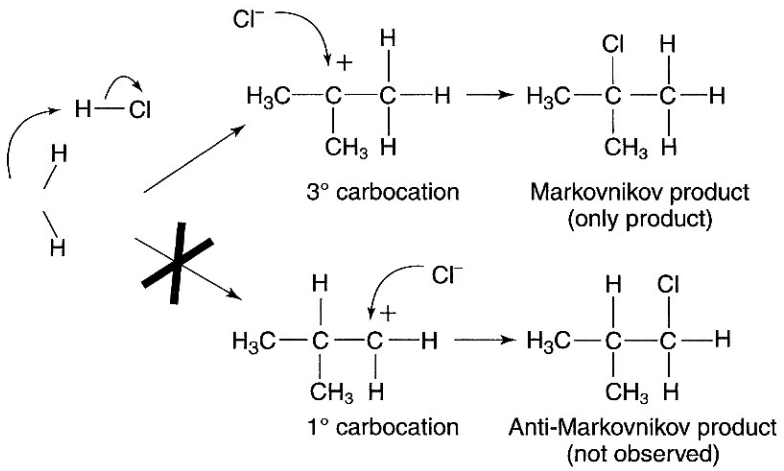
A double bond, however, can be protonated to generate two different cations, as shown in Figure 8-24. But which carbon in the double bond will receive the proton? (Or, alternatively, which side of the double bond will become positively charged?)

The Russian chemist Vladimir Markovnikov observed that alkenes are protonated on the least substituted carbon in the double bond, generating the carbocation on the most highly substituted carbon atom. In other words, *tertiary carbocations* (carbocations substituted by three alkyl groups and abbreviated 3÷) are preferred over *secondary carbocations* (cations substituted by two alkyl groups and abbreviated 2÷). Secondary carbocations in turn are favored over *primary carbocations* (1÷), those cations substituted by just one alkyl group.

e

car

product).



Because of this preference for more highly substituted carbocations, *halides add to the carbon that's most substituted with alkyl groups*. When addition occurs on the most substituted carbon, as in the reaction shown in Figure 8-24, the product is called the *Markovnikov product,* in honor of the the discoverer of this phenomenon.

Because this reaction favors one of two products — halide addition to the most substituted side of the double bond as opposed to halide addition to the least substituted side — this reaction is said to be *regioselective*. Regioselective reactions are those that prefer one constitutional isomer in a reaction to another (recall that constitutional isomers are molecules with the same molecular formula, but the atoms bonded in different ways).

But what accounts for this preference? Why are the more highly substituted carbocations more stable (and therefore preferable) to those cations with fewer alkyl substitutions? To understand this preference you need to look at the structure of the carbocation.

I'm positive: Carbocations

Carbocations are an unstable species because they leave the cationic carbon two electrons short of filling the atom's valence octet (and you know how much atoms hate that). In addition, the cationic carbon bears a full positive charge (which is something else that atoms don't like). The carbocation carbon is therefore highly electron deficient.

Helping a neighbor: Hyperconjugation

Alkyl substituents, however, can donate some electrons to the carbocation, thereby stabilizing it. For carbocations substituted with alkyl substituents, instead of the molecule localizing the full positive charge on just the one carbon atom, some of the positive charge is shared by the neighboring alkyl substituents. This sharing of charge is energetically preferable to having all of the charge localized on a single atom. Figure 8-25 shows the relative stability of primary, secondary, and tertiary carbocations.

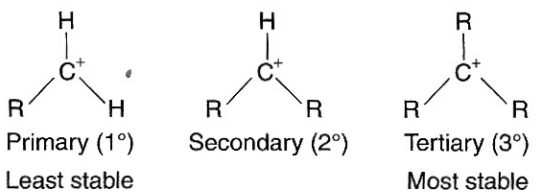


Figure 8-25: The relative stability of substituted carbocations.

Alkyl groups are able to donate electron density to the carbocation center through *hyperconjugation.* Hyperconjugation is organic-speak for the weak overlap that occurs between the empty *p* orbital on the carbocation and the σ bond of an adjacent alkyl C-H bond (or C-C bond), as shown in Figure 8-26. (Turn to Chapter 2 for a review of orbitals and bonds.) The more alkyl groups a carbocation center has, the more hyperconjugation takes place and the more the charge is shared; the more the charge is shared, the more stable the cation species is.

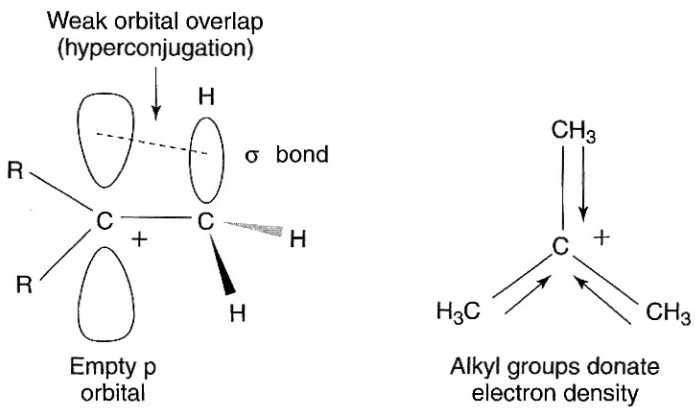


Figure 8-26: Hyperconjugation of neighboring alkyl groups.

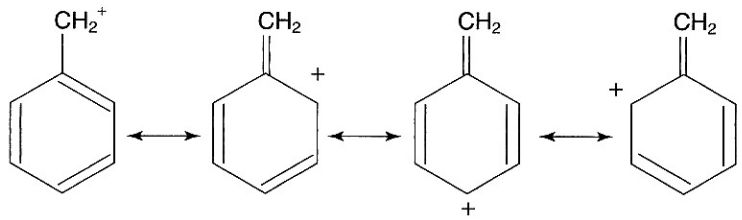
Resonance stabilization of carbocations

Carbocations are also stabilized by resonance. (See Chapter 2 for how to draw resonance structures.) Carbocations with resonance structures are more stable than carbocations without resonance structures, all else being equal. Thus, *benzylic* cations (cations next to a benzene ring), and *allylic* cations (cations adjacent to a double bond) are stabilized cations because of resonance delocalization of the positive charge onto other atoms, as shown in Figure 8-27.

Resonance structures stabilize molecules.



Allylic cation



Benzylic cation

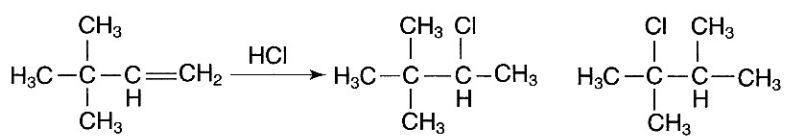
Figure 8-27: The resonance stabilization of allylic and benzylic cations.



The stabilities of carbocations can be approximated as follows (starting with the least stable and going to the most stable cation): primary cations < secondary cations ~ allylic cations < tertiary cations ~ benzylic cations.

Carbocation mischief: Rearrangements

Carbocations, like unsupervised children, have the capability of making a great deal of mischief. Take the reaction shown in Figure 8-28, for example. Reacting the alkene with hydrochloric acid yields the expected product only in small amounts; the major product is a rearranged alkyl halide.



Minor product Major product

Figure 8-28: The addition of HCl to an alkene.

How did this reaction occur? Through a carbocation rearrangement. Alkyl substituents or hydrogens can (and will) shift from a neighboring carbon to the carbocation center whenever doing so generates a more stable carbocation. In this example, protonating the double bond as shown in Figure 8-29 makes the secondary carbocation (which is more stable than the primary cation, the alternative in this reaction). Shifting a methyl group (along with the two electrons in the bond) from the adjacent carbon to the secondary carbocation shifts the cation to the more stable tertiary carbon. The halide then attacks the tertiary cation to make the rearranged product.

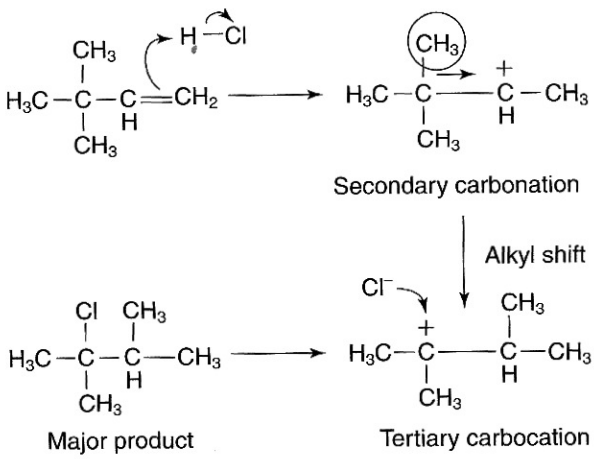


Figure 8-29: The mechanism of the carbocation rearrangement.



Spotting when these carbocation rearrangements may occur takes practice. When adjacent carbons to the cation center are highly substituted with alkyl groups, watch out for rearrangements.

Alkyl shifts can also open up small rings into larger ones, as shown in the reaction in Figure 8-30. Small rings (three- and four-membered rings) are less stable than medium-sized rings (those containing five to six carbons) because of the ring strain from the constricted bond angles created by the small rings (recall that sp^3 carbons prefer to have bonds at 109.5° angles from each other).



Number all of the atoms when working on ring expansion problems so you can keep track of all of the atoms and keep the charges on the correct atoms in the rearranged product.



Alkyl rearrangements occur for two primary reasons: 1) to make a more stable carbocation (for example to change a secondary carbocation to a tertiary carbocation), and 2) to relieve ring strain (for cations next to small rings).

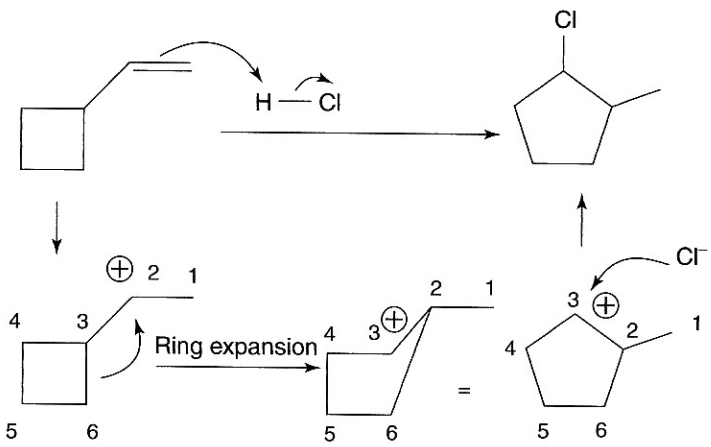


Figure 8-30: The carbocation rearrangement in a small ring.

Adding water across double bonds

Hydration, or adding water across a double bond to make an alcohol, is a reaction that's similar to the addition of a hydrohalic acid across a double bond. Two different reactions accomplish the hydration. The first reaction adds the alcohol (OH group) to the most substituted carbon on the double bond to make the Markovnikov product, and the complementary reaction puts the alcohol on the least substituted carbon in the double bond to make the anti-Markovnikov product.

Markovnikov addition: Oxymercuration-demercuration

To make the Markovnikov product where the alcohol adds to the most substituted carbon, you react the alkene with mercuric acetate ($Hg(OAc)_2$), followed by addition of sodium borohydride ($NaBH_4$). See Figure 8-31.

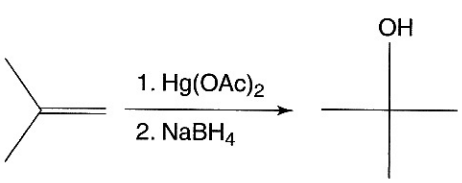


Figure 8-31: The oxymercuration-demercuration of an alkene.



The numbers over (or under) the reaction arrow indicate separate steps. In the case of oxymercuration-demercuration, the numbers specify that mercuric acetate is added first, followed by sodium borohydride. When no numbers are present over (or under) the arrow, this indicates that reagents are all added together in the same pot.

The mechanism for the oxymercuration-demercuration involves an attack of the double bond on the mercuric acetate to make a three-membered ring intermediate (called a *mercurinium ion*), as shown in Figure 8-32. Water then attacks the most highly substituted carbon to make the mercurial alcohol (after the loss of a proton). In the second step (when $NaBH_4$ is added), sodium borohydride replaces the mercuric portion with hydrogen (by a mechanism you don't need to know).

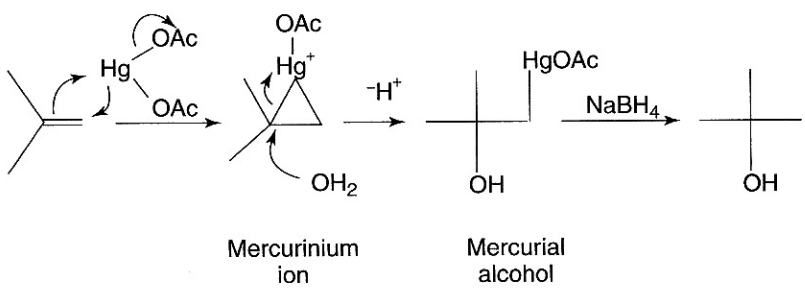


Figure 8-32: Oxymercuration-demercuration of an alkene.

Anti-Markovnikov addition: Hydroboration

With oxymercuration-demercuration, you have a reaction that converts alkenes into Markovnikov-product alcohols. To make the alcohol on the least-substituted carbon (called the anti-Markovnikov product) you use hydroboration, as shown in Figure 8-33. The addition of borane (BH_3) in tetrahydrofuran solvent (THF) to the alkene, followed by the addition of hydrogen peroxide (H_2O_2) and sodium hydroxide (NaOH), make the anti-Markovnikov alcohol.

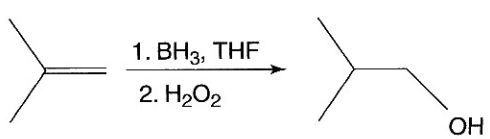


Figure 8-33: The hydroboration of an alkene.

The mechanism for hydroboration involves the cyclic transition state shown in Figure 8-34. Borane adds to the least substituted side of the double bond to make the alkyl borane. Because the addition is concerted (both the hydrogen

and BH_2 are added simultaneously), the borane and hydrogen must add to the same face of the carbon-carbon bond (two groups adding to the same face of a double bond is called *syn addition*). In the second step, hydrogen peroxide (H_2O_2) in the presence of sodium hydroxide (NaOH) substitutes a hydroxyl group (OH) for the boryl unit (BH_2) to make the anti-Markovnikov alcohol (in a mechanism you don't need to know).



Recall that *syn addition* is when two groups add to the same face of a double bond, and *anti addition* is where two groups add to opposite faces of a double bond. Therefore, syn addition to cycloalkenes results in the two added groups being cis to each other, and anti addition to cycloalkenes results in the two added groups being trans to each other.

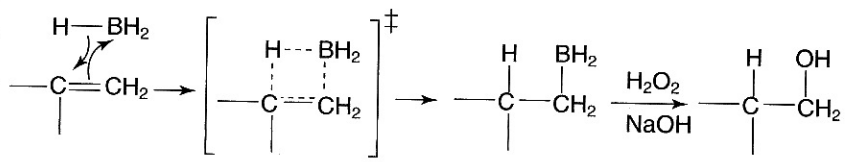


Figure 8-34: Hydroboration of an alkene.

A double shot: Dihydroxylation

While you can add one hydroxyl group to a double bond using either oxymercuration-demercuration or hydroboration, you can also add two hydroxy groups across a double bond using osmium tetroxide (OsO_4) in the presence of hydrogen peroxide (H_2O_2), as shown in Figure 8-35. This reaction is called a dihydroxylation.

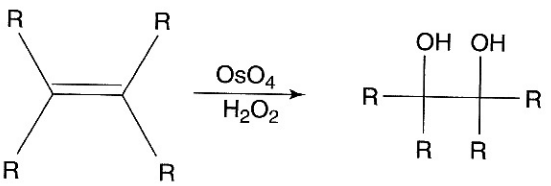


Figure 8-35: Dihydroxylation of an alkane.

The mechanism for dihydroxylation involves the reaction of the alkene and the osmium tetroxide to generate a five-membered cyclic osmate ester, as shown in Figure 8-36. Hydrogen peroxide (H_2O_2) regenerates the osmium tetroxide catalyst and makes the diol (a *diol* is a molecule with two hydroxyl [OH] groups) by a mechanism you probably don't need to know. Because both oxygens in the osmium tetroxide are added to the same face of the double bond, both hydroxyl groups end up on the same side of the carbon-carbon bond (that is, they're added via syn addition).

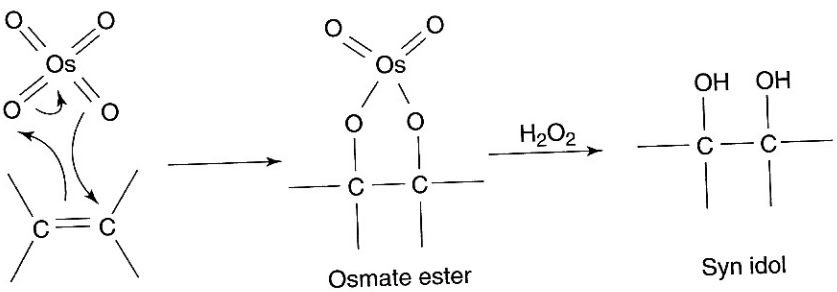


Figure 8-36: The mechanism for the hydroxylation of an alkene.

Double the fun: Bromination

Alkenes react rapidly with bromine (Br_2) or chlorine (Cl_2) in carbon tetrachloride (CCl_4) solvent to make a dihalide, as shown in Figure 8-37. This reaction is, in fact, used as a test to see whether an unknown compound contains an alkene, because the blood-colored bromine (Br_2) turns white when it reacts with alkenes.

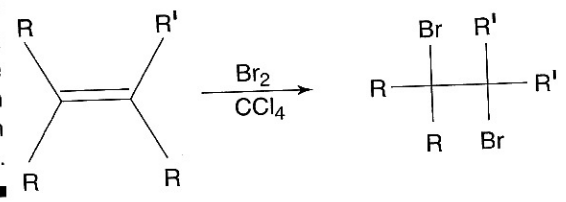


Figure 8-37: The bromination of an alkene.

The mechanism for bromination is somewhat unusual. Reaction of the alkene and bromine results in a cyclic three-membered intermediate called a bromonium ion (or chloronium ion for chlorine), plus the free halide, as shown in Figure 8-38. The free halide then attacks the backside of the bromonium ion to make the dibromide with anti-stereochemistry.

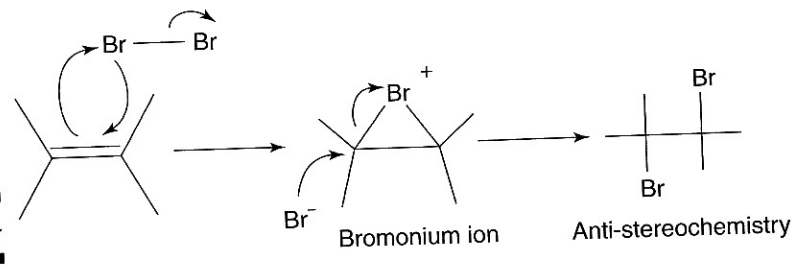
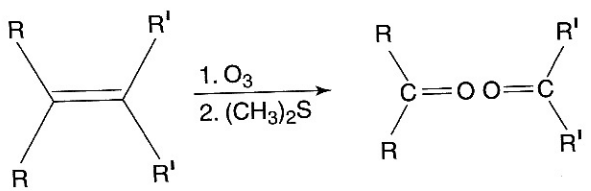


Figure 8-38: The mechanism for the bromination of an alkene.

Chopping up double bonds: Ozonolysis

Ozonolysis is a way of cleaving carbon-carbon double bonds into two fragments using oxone (O_3) as a reagent. The fragments formed are either aldehydes or ketones, depending on the nature of the R groups attached to the double bond (see Figure 8-39). If both R groups on one side of the double bond are alkyl groups, that side of the double bond will become a ketone fragment; if only one R group is an alkyl group and the other R is a hydrogen, that side of the double bond will become an aldehyde fragment.

The ozonolysis of an alkene.



A quick way of determining the products of ozonolysis is to visually snip the double bond as shown in Figure 8-40, and then to cap both sides with oxygens to make the carbonyl compounds.

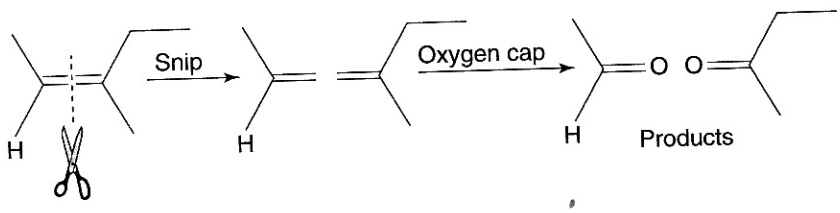


Figure 8-40: Determining products of ozonolysis.



A common exam problem is one that asks you to determine the structure of the starting alkene given the products of ozonolysis. If you remember how to determine the products of ozonolysis and then work backward from that reaction (snip off the oxygens, and then smoosh the two pieces together), you get the starting alkene.

Double-bond cleavage: Permanganate oxidation

Permanganate oxidation, shown in Figure 8-41, performs essentially the same reaction as ozonolysis, except that permanganate is a somewhat stronger oxidizing reagent than ozone. In permanganate oxidation, all products that would

have become aldehydes using ozonolysis are further oxidized to carboxylic acids with potassium permanganate ($KMnO_4$); ketone fragments stay the same.

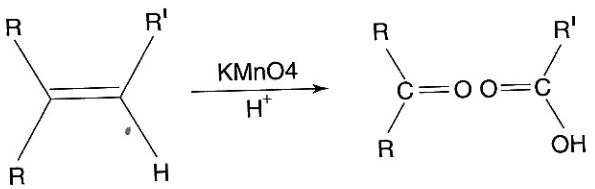


Figure 8-41: The permanganate oxidation of an alkene.

Making cyclopropanes with carbenes

Alkenes can be converted into cyclopropane rings by reacting with an unusual species called a carbene, as shown in Figure 8-42.

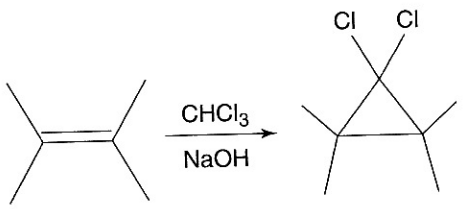


Figure 8-42: Making a cyclopropane ring from an alkene.

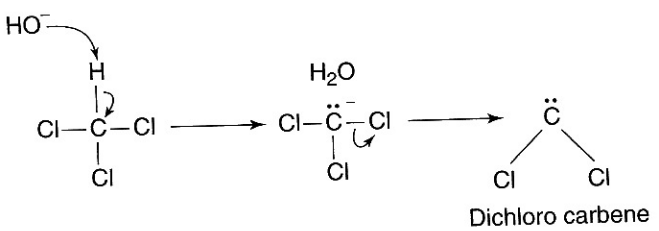


Figure 8-43: Making dichlorocarbene.

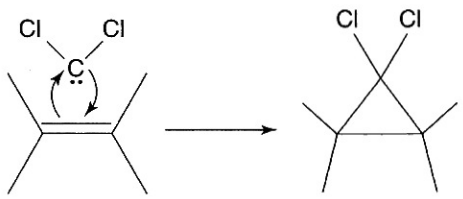


Figure 8-44: The dichlorocarbene addition to an alkene.

Making cyclopropanes: The Simmons-Smith reaction

A good way to make unsubstituted cyclopropanes from carbon-carbon double bonds is by using the Simmons-Smith reaction, shown in Figure 8-45. While the carbene methylene (H_2C:) is not actually made in this reaction, a zinc species (ICH_2ZnI) is used that reacts as if it were the carbene methylene. Because the reagent behaves like a carbene but really isn't one, this zinc species is said to be *carbenoid* (carbine-like).

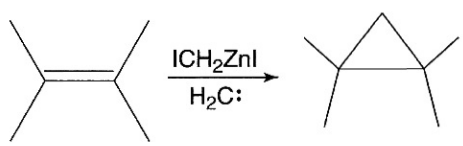


Figure 8-45: The Simmons-Smith reaction.

Making epoxides

Epoxides are ethers in three-membered rings. They're valuable synthetic reagents, and are used in epoxy glues. Epoxides can be made by reacting an alkene with a peroxy acid (a carboxylic acid with an extra oxygen), as shown in Figure 8-46.

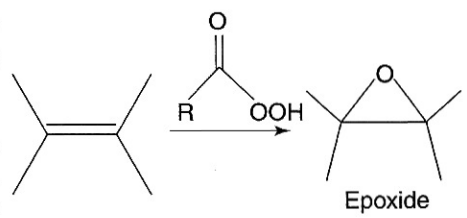


Figure 8-46: The epoxidation of an alkene.

Adding hydrogen: Hydrogenation

Alkenes can be converted into alkanes by hydrogenation. Passing hydrogen gas through a solution containing a catalyst — usually palladium on carbon, (Pd/C) or platinum (Pt) — and the alkene causes hydrogen to be added across the double bond in a syn addition (see Figure 8-47).

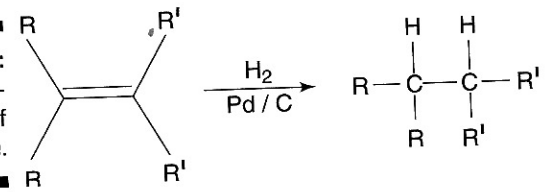


Figure 8-47: The hydrogenation of an alkene.

Chapter 9

Takes Alkynes: The Carbon-Carbon Triple Bond

As a functional group, alkynes are somewhat less common (and, truth be told, somewhat less important) than alkenes, but they still have some very interesting features and reactivities that are unique to them.

Alkynes are molecules that contain carbon-carbon triple bonds. As might be expected, the reactivities and properties of alkynes are very similar to those of alkenes, although a few interesting differences between the two types of molecules also exist. In this chapter, I discuss the properties of alkynes, show you how to name alkynes, and cover the fundamental reactions that form alkynes and convert them into other functional groups.

Naming Alkynes

Alkynes are named under the systematic nomenclature scheme in the same way that alkenes are (refer to Chapter 8), except that instead of the name ending with the suffix *-ene,* the names of alkynes end with the suffix *-yne.* As with alkenes, a number in the prefix is used to indicate the position of the alkyne in the molecule, as demonstrated in Figure 9-1.

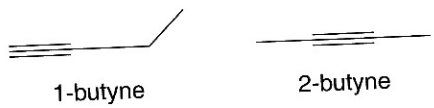
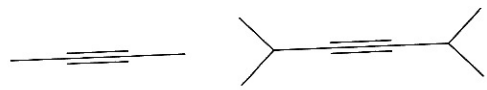


Figure 9-1: The names of two alkynes.

Alkynes are often known by their common names; these common names are derivatives of the simplest alkyne, acetylene. Under the common name system, the two R groups are named as substituents of acetylene (see Figure 9-2 for some examples). An alkyne with two methyl groups would be dimethyl acetylene, an alkyne with two isopropyl groups, diisopropyl acetylene, and so on.



Alkyne	HC≡CH		
IUPAC Name	Ethyne	2-butyne	2,5-dimethyl-3-hexyne
Common Name	Acetylene	Dimethyl acetylene	Diisopropyl acetylene

Figure 9-2: The common names of some alkynes.

Seeing Alkyne Orbitals

Alkyne carbons, by having only two substituents, are *sp* hybridized, and so have linear bonds that are oriented at 180° to each other. (See Chapter 2 for more on hybridization.) The triple bond in an alkyne is made up of one sigma bond and two pi bonds. The two pi bonds result from the side-by-side overlap of the two *p* orbitals on each carbon atom (see Figure 9-3). As in the case with alkenes, the pi bonds are the reactive bonds in alkynes.

The overlapping *p* orbitals that make up the two pi bonds keep the alkyne in a linear geometry. Because alkynes have linear geometries, they're drawn in a straight line, as shown in Figure 9-4.

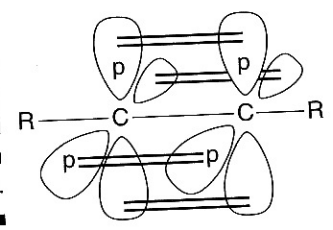


Figure 9-3: The pi bonds in an alkyne.

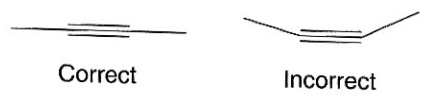


Figure 9-4: The correct way to draw an alkyne.

Alkynes in Rings

Because alkynes prefer linear geometries, alkynes in small rings are highly unstable. Small- to medium-sized cycloalkynes have bonds that must stretch out of their preferred geometries, and so inflict a good amount of ring strain on the atoms. Imagine grabbing your leg (which, like an alkyne, prefers to be linear) and touching your big toe to your nose, forming a ring with your body. The strain on your body is similar to the strain an alkyne feels. Just as you probably wouldn't feel particularly stable forming a ring by touching your toe to your nose (how long could you hold it?), alkynes in rings smaller than seven carbons are too unstable to be made or isolated. Cycloheptyne, the smallest cycloalkyne isolated, has been characterized, but it is highly reactive (see Figure 9-5). Alkynes in rings containing more than seven carbons can be made and are fairly stable compounds.

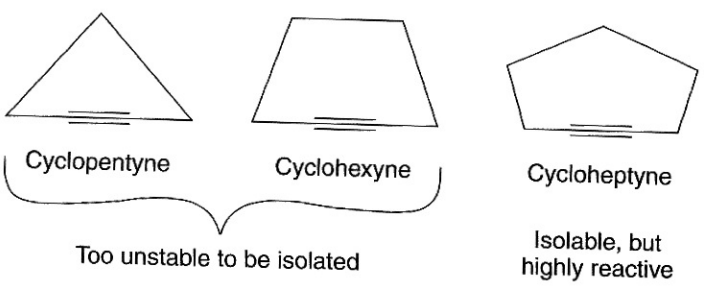


Figure 9-5: The relative stabilities of alkynes in small rings.

Making Alkynes

To make alkynes, two reactions are readily available, one that you might expect based on reactions that form alkenes, and another one that you might not expect based on what you know about the chemistry of alkenes.

Losing two: Dehydrohalogenation

To form alkenes (see Chapter 8), you can react one equivalent (unit) of base with an alkyl halide to eliminate one equivalent of acid and form the alkene. You might expect that to make an alkyne, you might treat a dibromide with two equivalents of base, eliminating two equivalents of acid to make the alkyne. This is indeed the case, as shown in Figure 9-6. Usually, the base that's used is the strong base sodium amide ($NaNH_2$, sometimes called sodamide), although sodium hydroxide (NaOH) can also be used.

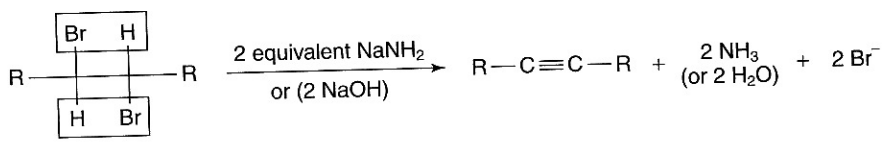


Figure 9-6: The double dehydrohalogenation of an alkyl dihalide.



Recall that dibromides can be made by reacting an alkene with bromine (Br_2). This is a convenient way to convert alkenes into alkynes: Brominate the alkene using Br_2 to make the dibromide, then treat the dibromide with two equivalents of base to make the alkyne.

Coupling alkynes: Acetylide chemistry



Figure 9-7: Making the acetylide anion.

This acetylide ion is a very useful *nucleophile* (or "nucleus lover"), and will react with primary alkyl halides to form a new, internal alkyne as shown in Figure 9-8. This reaction is highly useful because it forms a carbon-carbon bond where one did not exist before. Note, however, that only primary alkyl halides can be used in this reaction; that is, the halide must be attached to a methylene (CH_2) unit. Secondary and tertiary alkyl halides will not react in this way.

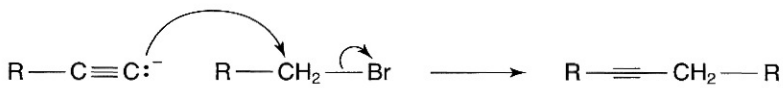


Figure 9-8: Acetylide addition.

Alkyne reactions are similar to those of the alkenes, and these reactions use reagents similar to those used in alkene reactions. Alkynes can form a variety of functional groups, as shown in Figure 9-9.

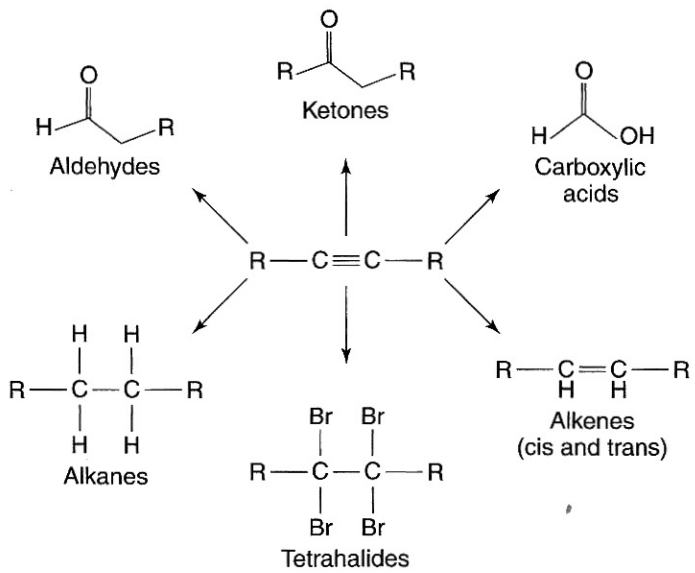


Figure 9-9: Some of the compounds that can be made from alkynes.

Brominating alkynes: Double the fun

Bromine reacts with the pi bond in alkynes to make the dibromide via the same mechanism as bromine addition to alkenes. (Do you recall the mechanism of

the alkene reaction? Think "bromonium ion," and see Chapter 8 if you need to refresh your memory.) Because there are two pi bonds in an alkyne, two equivalents (units) of bromine can be added to make a tetrabromide, as shown in Figure 9-10.

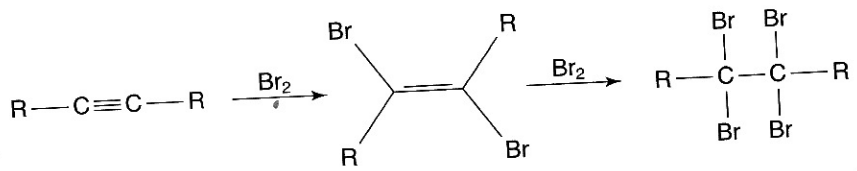


Figure 9-10: The bromination of an alkyne.

Saturating alkynes with hydrogen

Alkynes can also be reduced to alkanes by bubbling two equivalents of hydrogen gas (H_2) over the alkyne in the presence of a metal catalyst as shown in Figure 9-11. This catalyst is usually palladium on carbon (Pd/C), but platinum (Pt) is also sometimes used.

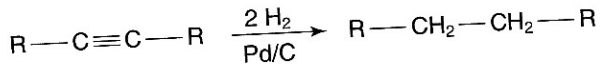


Figure 9-11: The saturation of an alkyne with hydrogen.

Adding one hydrogen molecule to alkynes

Stopping the reaction of alkynes with hydrogen at the alkene stage is possible because alkenes are somewhat less reactive than alkynes, but this reaction requires a special catalyst. To reduce an alkyne to the cis alkene (see Chapter 8 for more about cis and trans alkenes), you use Lindlar's catalyst, which is a cocktail of palladium (Pd) powder made less reactive with added lead (Pb) and quinoline (C_9H_7N). (In reaction diagrams, instead of writing out all of the components of the catalyst, chemists often write "Lindlar's catalyst" over or under the arrow.) Lindlar's catalyst is not as reactive as palladium on carbon (Pd/C) and generates the cis alkene, as shown in Figure 9-12.

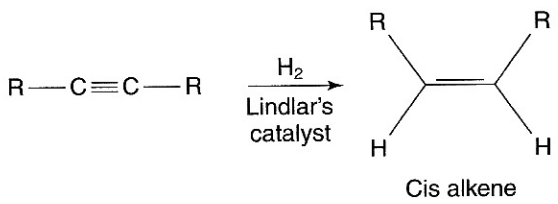


Figure 9-12: Using Lindlar's catalyst to make cis alkene.

To convert an alkyne to the trans alkene, you use sodium metal (Na) in liquid ammonia (NH_3), as shown in Figure 9-13.

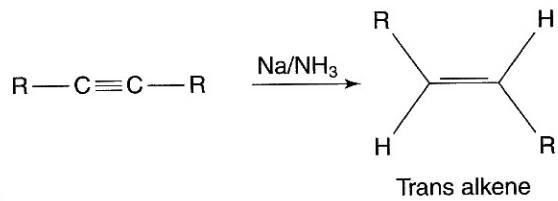


Figure 9-13: Making a trans alkene from an alkyne.

Oxymercuration of alkynes

Reacting alkynes with mercury, water, and acid, you might expect the reaction to make the alcohol on the double bond, just as mercuric acetate reacts with alkenes to make the Markovnikov alcohol (see Chapter 8 for a review of Markovnikov products and the oxymercuration of alkenes). Indeed, the Markovnikov *enol* (an alcohol on a double bond) is formed in which the alcohol group is placed on the more-substituted carbon. However, enols are unstable and rapidly convert into ketones, as shown in Figure 9-14.

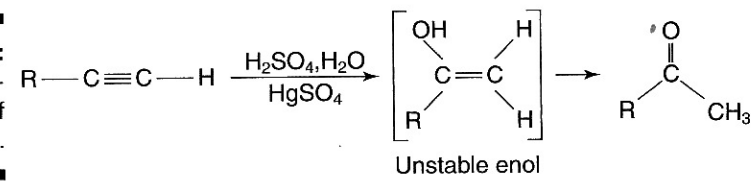


Figure 9-14: The oxymercuration of an alkyne.



The term enol is a combination of the suffixes *-en* (from alk*ene*) and *-ol* (from alcoh*ol*).

The reaction that converts the enol into the ketone is called a *tautomerization reaction,* and both the enol and the ketone are considered *tautomers* of each other. Tautomers are molecules that differ only in the placement of a double bond and a hydrogen.

Hydroboration of alkynes

The hydroboration reaction of alkynes works in the same way as the hydroboration reaction of alkenes, and forms the anti-Markovnikov product. In the case of the hydroboration of alkynes, the product is an enol with the alcohol group on the least-substituted carbon, as shown in Figure 9-15. As with oxymercuration reaction, this enol is unstable and tautomerizes to the aldehyde.

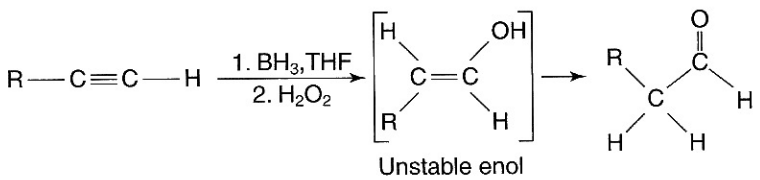


Figure 9-15: The hydroboration of an alkyne.



Oxymercuration and hydroboration of carbon-carbon triple bonds are useful primarily with terminal alkynes because with terminal alkynes, you get only a single product (with hydroboration, you get the aldehyde; with oxymercuration, you get the ketone). With internal alkynes, both sides of the alkyne are equally substituted, so water can be added equally well to either side of the triple bond, so these reactions yield mixtures of two products.

Part III
Functional Groups

COLLIDE.

In this part . . .

You get to the meat and potatoes of organic chemistry: the functional groups. Functional groups are the interesting reactive portions of organic molecules. In these chapters, you see different functional groups (such as alcohols, halides, and aromatics) and how they react to form other compounds.

Chapter 10

Replacing and Removing: Substitution and Elimination Reactions

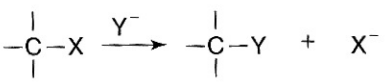
- Considering nucleophiles and leaving groups
- Seeing first-order substitution
- Discovering first-order and second-order elimination reactions
- Distinguishing substitution and elimination reactions

Although you see countless reactions in organic chemistry, you usually don't sweat the details too much, details like what kinds of solvents are ideal for that reaction, or typical side pathways that lead to undesirable byproducts. The substitution and elimination reactions are exceptions, because these are some of the most widely applicable and versatile reactions that you see in organic chemistry. As such, they deserve a closer look. In this chapter, I present the substitution and elimination reactions, and show you how to recognize these types of reactions. With just these two reaction types, you can synthesize more organic molecules than you can shake a stick at.

Group Swap: Substitution Reactions

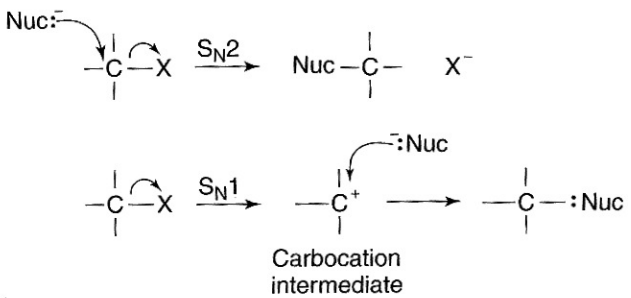
Substitution reactions follow the form shown in Figure 10-1. The overall reaction is fairly simple — one group simply substitutes for another in the reaction.

Figure 10-1: A substitution reaction.



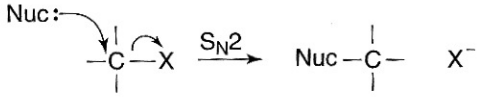
Two mechanisms for substitution are possible, the *S_N1 mechanism,* and the *S_N2 mechanism,* and they're shown in Figure 10-2. So how do you know which mechanism will occur for a given substitution reaction? The answer, unfortunately, is, "It depends." It depends on the solvent, the nature of the substrate, and the substituting group (called the *nucleophile,* or nucleus lover, sometimes abbreviated Nuc). To figure out which mechanism will occur, you need to see the details of each mechanism.

Figure 10-2: Two different substitution mechanisms.

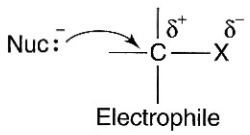


Seeing Second-Order Substitution: The S_N2 Mechanism

Figure 10-3: The S_N2 mechanism.



Why does the nucleophile attack the carbon? One way to think of this reaction is in terms of the attraction between opposite charges. The carbon-leaving group bond (C-X) is polarized; that is, the electronegative leaving group pulls electron density away from the carbon to which it's attached, leaving the carbon with a partially positive charge, as shown in Figure 10-4. (See Chapter 2 for more on electronegativity.) Therefore, the molecule that contains the leaving group (called the *substrate*) acts as an *electrophile* (an electron lover). Nucleophiles (electron-rich species that love nuclei) attack the partially positive carbon, in the same way that two oppositely charged magnets scooch together.



If you understand nucleophile-electrophile attraction in this way, you can understand many, many organic reactions. The basic templates for these reactions are the same: Some electron-rich atom with a lone pair (a nucleophile) attacks an electron-poor atom (an electrophile). The details change, but that's pretty much the gist of it.

How fast? The rate equation for the S_N2 reaction

The rate of the S_N2 reaction follows the rate equation:

$$\text{rate} = k[\text{substrate}][\text{nucleophile}]$$

Looking at this rate equation, you see that the concentration of both the substrate *and* the nucleophile determine the rate of the S_N2 reaction, making the S_N2 reaction second order (thus, the "2" in S_N2).

The reaction diagram for the S_N2 mechanism is shown in Figure 10-5. A *reaction diagram* displays the energy (labeled E) as a function of time. Every reaction has at least one energy "hill" that must be climbed to transform the starting materials into the products; this "hill" is a barrier called the *activation energy*, or *Ea*. The activation barrier is the minimum amount of energy that needs to be supplied to transform the starting material into product.

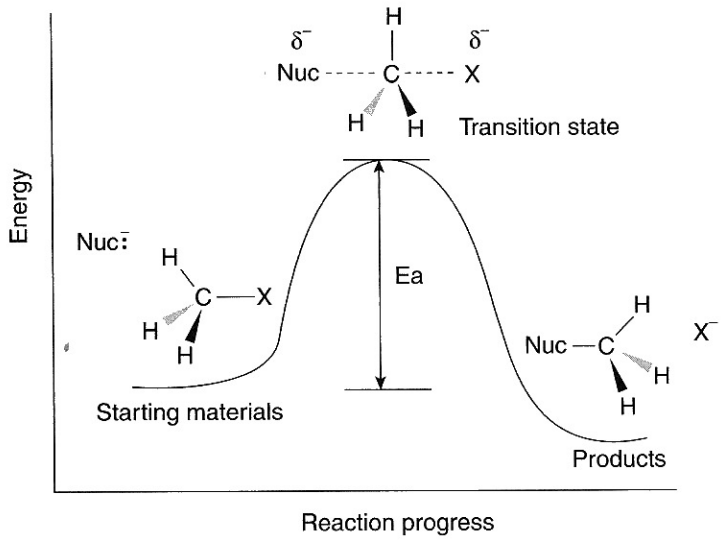


Figure 10-5: The S_N2 reaction diagram.

The size of the activation barrier determines the rate of the reaction. If the reaction only has to climb a very small energy hill, the reaction will proceed quickly. If the energy hill is high, the reaction will occur much more slowly, just as an athlete runs faster over a small hill than over a mountain.



The top of the energy hill is the *transition state* of the reaction. This is the point at which the starting materials are midway through the reaction, when the reactants are at their highest energy level, and when the bonds in the reactants are partially broken and partially formed. A transition state cannot be isolated; however, it's not a long-lived intermediate, but simply a transition between the starting materials and products. It's just a point on the road to transforming one material into the next. A reaction passes through the transition state faster than a chemistry professor can mark an X on an exam.

Effect of the substrate on the S_N2 reaction

A nucleophile approaching a substrate in order to undergo an S_N2 reaction is a lot like a fan approaching a celebrity to get an autograph. If a celebrity has no bodyguards, the fan can easily approach and ask for the autograph. With one bodyguard (I'll call these bodyguards "R groups"), the fan has a little more difficulty slipping by the bodyguard, but getting the autograph is still doable. The fan may need to wait until the bodyguard lets his guard down and allows

the fan to slip past. With two R group bodyguards, the fan would have an even harder time (or a longer wait) before he or she could slip through to the celebrity. But with three bodyguards blocking all lines of approach to the celebrity, the fan might as well forget about getting that precious autograph.

R groups on the carbon that contains the leaving group act as bodyguards, and hinder the approach of the nucleophile, as shown in Figure 10-6. Therefore, S_N2 reactions work best with methyl and primary substrates, when the carbon containing the leaving group has no R group bodyguards attached to it (in the case of a methyl substrate) or just one (in the case of a primary substrate). Reactions with substrates that contain two R group bodyguards (secondary substrates) do proceed, but these reactions take place at a slower rate than reactions with primary substrates. But with tertiary substrates (substrates in which the carbon that contains the leaving group has three R groups attached to it), the S_N2 reaction says, "No dice," and you get no reaction. Why? Everything comes back to the mechanism. In the S_N2 mechanism, the nucleophile attacks the *backside* of the substrate. With three big fat bulky R groups blocking the rear approach, the nucleophile can't get close enough to attack the carbon. Such blocking by bulky groups is called *steric hindrance,* using organic-speak. Because of such steric hindrance, you won't see an S_N2 reaction on a tertiary substrate.

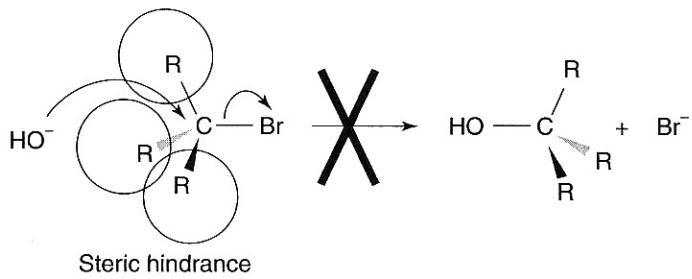


Figure 10-6: Steric hindrance can prevent an S_N2 reaction.



S_N2 reactions prefer methyl (CH_3X) over primary substrates ($R\text{-}CH_2\text{-}X$), but primary over secondary substrates (R_2CHX). S_N2 reactions don't work with tertiary substrates (R_3CX).

Needs nucleus: The role of the nucleophile

Because the concentration of the nucleophile is included in the rate equation of the S_N2 reaction, a good nucleophile is required. That leads to the somewhat sticky question: What makes a good nucleophile? Unfortunately, that

question can't be answered precisely, because the strength of a nucleophile can change by varying the solvent or reaction conditions. Still, some general rules about nucleophile strength can be applied.



Any molecule with a lone pair of electrons to donate can act as a nucleophile. The strength of a nucleophile (or the *nucleophilicity*, using organic-speak) generally goes hand-in-hand with basicity. A strong base is usually a strong nucleophile and vice-versa. But basicity and nucleophilicity are not the same things. Basicity refers to the ability of a molecule to pluck off a proton, and is defined by the base's equilibrium constant; nucleophilicity refers to the ability of a lone pair to attack a carbon on an electrophile.

When wouldn't basicity and nucleophilicity coincide? Usually, these don't coincide when you have bases/nucleophiles substituted with bulky groups. For example, both methoxide (CH_3O^-) and t-butoxide ($(CH_3)_3CO^-$), shown in Figure 10-7, are strong bases, but methoxide is a good nucleophile while t-butoxide is not. The reason for this difference is that t-butoxide has three bulky methyl groups that hinder approach to the substrate (another example of steric hindrance). Therefore, even though t-butoxide is a strong base, it's a poor nucleophile.

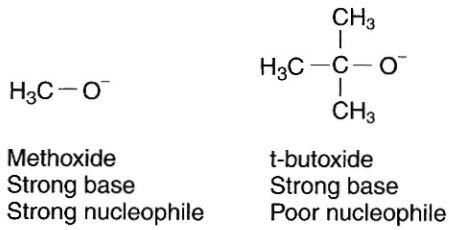


Figure 10-7: The nucleophilicity of two strong bases.



Steric hindrance decreases nucleophilicity.

In addition to the basicity of a molecule, two other major factors can help you compare the nucleophilicities of molecules:

Seeing the S_N2 reaction in 3-D: Stereochemistry

In the S_N2 reaction, the nucleophile approaches from the backside of the substrate. Therefore, in the product, the three groups on the carbon have inverted, like an umbrella blown inside out by the wind. With the S_N2 reaction, then, you get *inversion of stereochemistry* (see Chapter 7 for more on stereochemistry). For example, with the reaction of 2-bromobutane and hydroxide (see Figure 10-8), the chiral center has an *S* configuration in the starting material but an *R* configuration in the product as a result of the inversion of configuration in the S_N2 reaction.



The S_N2 reaction leads to an inversion of the stereochemistry.

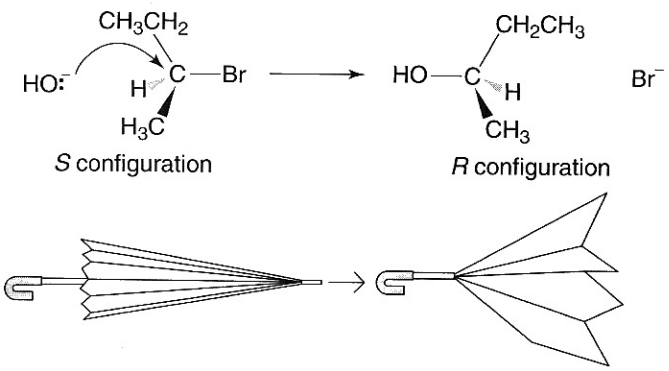


Figure 10-8: The S_N2 reaction of 2-bromobutane.

Seeing solvents effects

The choice of solvent also affects the S_N2 substitution reaction. Not all solvents are created equal; some solvents work better than others in a given reaction. In the S_N2 reaction, the preferred solvents are those that are both polar (see Chapter 2) and *aprotic*. Protic is organic-speak for solvents that contain O-H or N-H bonds; these solvents include alcohols, water, and amines. Aprotic solvents have no N-H or O-H bonds. Good polar aprotic solvents for the S_N2 reaction include DMSO (dimethyl sulfoxide), CH_2Cl_2 (dichloromethane), and ethers (R-O-R).

Why do you need aprotic and not protic solvents for the S_N2 reaction? Protic solvents tend to form a solvent "cage" around the nucleophile, as shown for the chloride ion caged by water in Figure 10-9. This cage makes the nucleophile

less nucleophilic. A nucleophile in a protic solvent is like a college student surrounded by televisions — it doesn't feel particularly inclined to go out and do the work that needs to be done. Polar solvents that are aprotic still have the ability to dissolve the polar reactants (because "like dissolves like" as you discovered in your first year of chemistry), but these polar aprotic solvents don't cage the nucleophile, and thus they don't make the nucleophile less nucleophilic.



Protic solvents decrease nucleophilicity in S_N2 reactions.

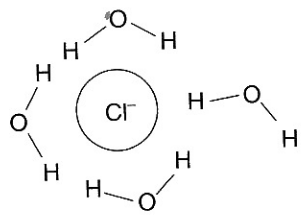


Figure 10-9: The solvent cage formed by the protic solvent (water).

Surrounded nucleophile (less nucleophilic)

I'm outta here: The leaving group

Another requirement of the S_N2 reaction is that the substrate needs to have a good leaving group. The leaving group is the piece that's displaced by the nucleophile (often labeled X). Good leaving groups are typically weak bases, and weak bases are the conjugate bases of strong acids (see Chapter 5 for more on acids and bases). Therefore, if you can find a strong acid and deprotonate it, you've probably found a good leaving group. The hydrohalic acids (HBr, HCl, and so on) are strong acids, so the halides (like I^-, Br^-, Cl^-) are excellent leaving groups (Fluoride, F^-, however, is an exception, as it is a bad leaving group). The halides, in fact, are the most common leaving groups in S_N2 reactions. Another good leaving group is tosylate. Tosylate is the conjugate base of the strong acid p-toluenesulfonic acid, and is one of the best leaving groups available (better than all of the halides). Figure 10-10 shows the most common leaving groups, and ranks them from best to worst.



Hydroxide ion (OH^-), alkoxides (RO^-), *and amide ion,* (NH_2^-), *are terrible leaving* groups because they're strong bases. Show them as leaving groups at your own risk. Because these groups are bad leaving groups, you won't see an S_N2 reaction on an ether (which is why you can use ethers as solvents in S_N2 reactions), alcohol, alkyl fluoride, or an amine.

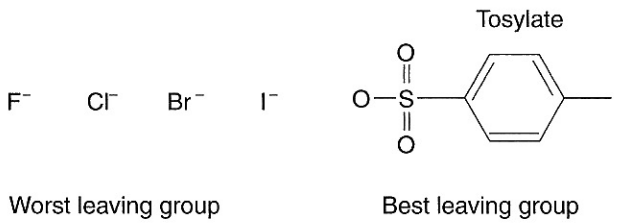


Figure 10-10: Leaving groups for the S_N2 reaction.

First-Order Substitution: The S_N1 Reaction

The other substitution mechanism is the S_N1 mechanism, and is shown in Figure 10-11. The S_N1 reaction proceeds in two steps. In the first step, the leaving group decides to pack its bags and take off, leaving a carbocation intermediate. Then, the nucleophile attacks the carbocation to make the substituted product.

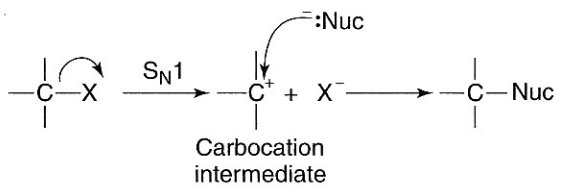


Figure 10-11: The S_N1 mechanism.

How fast? The rate equation for the S_N1 reaction

The rate for the S_N1 reaction follows the rate equation: rate = k[substrate].

You might be surprised to see that, unlike the case in the S_N2 reaction, the concentration of the nucleophile is not included in the rate equation for the S_N1 reaction. The rate equation is first order (thus the "1" in S_N1) and depends only on the concentration of the substrate. Why is the nucleophile not included? You can see why by looking at the reaction diagram, shown in Figure 10-12.

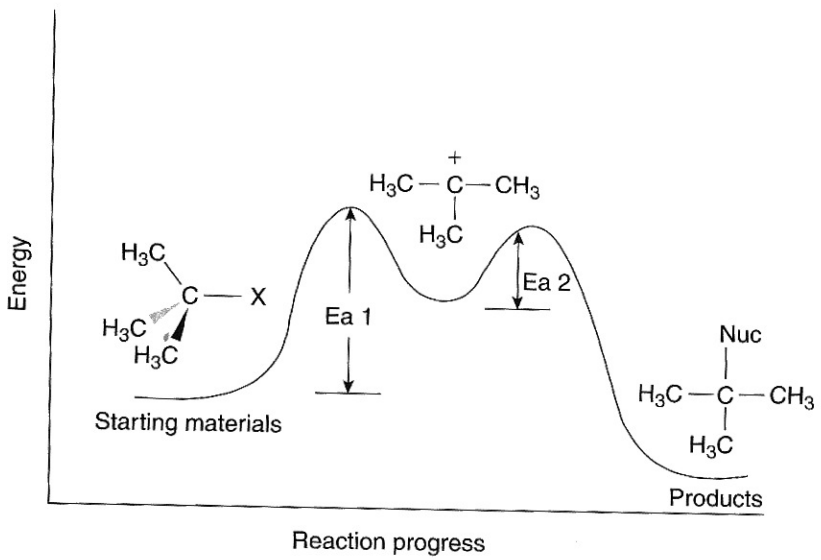


Figure 10-12: The S_N1 reaction diagram.

From the reaction diagram, you see that two hills need to be climbed to transform the starting materials into the product. The first hill is the tallest one, and is the energy barrier for the step in which the leaving group makes like a tree and gets the heck out of there, forming the carbocation. The second step, the attack of the nucleophile on the carbocation, involves a smaller energy hill. Because the first step has the highest activation barrier, it's called the *rate-determining step*.

u

effect on the rate of

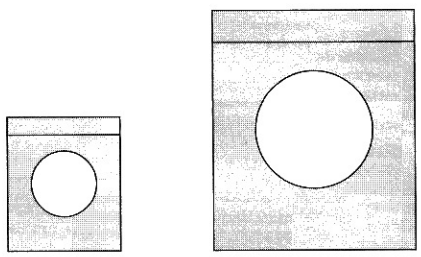


Figure 10-13: With this tiny washer, washing is the rate-determining step.

Seeing good S_N1 substrates

Good substrates for the S_N1 reaction are different from those that are good for the S_N2 reaction. Good substrates for the S_N1 reaction will be substrates that form a stable carbocation upon releasing the leaving group. If you lower the energy of the cation intermediate, you lower the activation energy, and thus speed up the reaction. So, to find good substrates for the S_N1 reaction you look for those that will lead to a stable intermediate carbocation.

Recall the features that contribute to carbocation stability (refer to Chapter 8 if you need a refresher on carbocations). Carbocations are stabilized by the presence of alkyl groups or by resonance. Thus, tertiary substrates form more stable carbocations than secondary or primary substrates. As a result, tertiary substrates are better S_N1 substrates than secondary substrates, which in turn are better S_N1 substrates than primary substrates (see Figure 10-14). Substrates with the ability to stabilize the cation through resonance are also good S_N1 substrates; these substrates include benzylic and allylic substrates.



Good S_N1 substrates are those that can make stable carbocation intermediates.

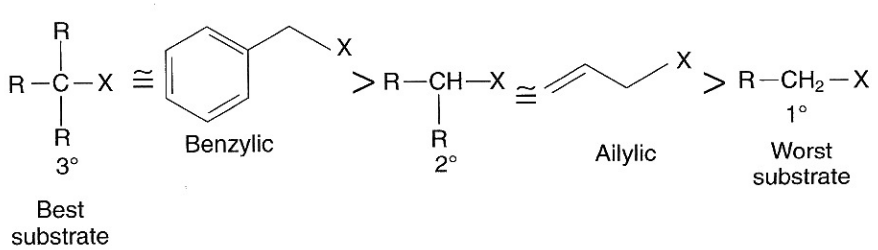


Figure 10-14: Substrates for the S_N1 reaction.

Seeing solvent effects on the S_N1 reaction

While S_N2 reactions prefer aprotic solvents, S_N1 reactions prefer protic solvents. This preference comes from the ability of protic solvents to stabilize the intermediate carbocation (as shown in Figure 10-15), lowering the energy hill for the rate-determining step. Recall that in the S_N2 reaction you don't want protic solvents because they decrease the nucleophile strength. In the S_N1 reaction, the strength of the nucleophile has no effect on the rate, so protic solvents (like alcohols and water) are excellent for S_N1 reactions. You generally won't see S_N1 reactions in aprotic solvents.



Protic solvents stabilize carbocations in S_N1 reactions.

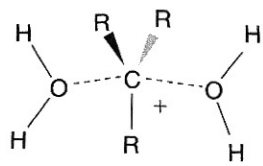


Figure 10-15: The stabilizing interaction of a protic solvent (water) with a cation.

Stereochemistry of the S_N1 reaction

Stereochemistry in the S_N1 reaction is not as clear-cut as it is in the S_N2 reaction. The intermediate in the S_N1 reaction is a carbocation, which is sp^2 hybridized. As a result, these carbocations are planar, and have an empty *p* orbital. The empty p orbital could be attacked equally well by the nucleophile's lone pair from either the top or the bottom of the carbocation, as shown in Figure 10-16. Therefore, you get about a 50:50 mixture of enantiomers from the S_N1 reaction, which is called a *racemic mixture* (see Chapter 6).

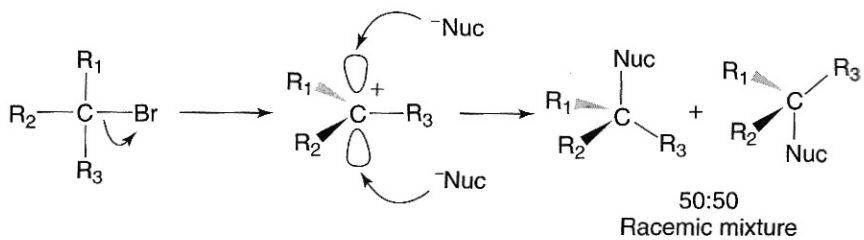


Figure 10-16: The S_N1 reaction of a tertiary alkyl halide.

S_N1 reactions give racemic products.

Other fun facts about the S_N1 reaction

Because the strength of the nucleophile is unimportant, S_N1 reactions work best with weak nucleophiles. The S_N1 reaction requires a good leaving group (like a halide or tosylate), as the S_N2 reaction does. An important detail to remember about the S_N1 reaction is the consequence of going through a carbocation intermediate. Recall that carbocations are mischievous little devils, and will rearrange if doing so will lead to a stable cation (see Chapter 8 for more on carbocations). As a result, you occasionally see carbocation rearrangements in the S_N1 reaction.

Table 10-1 is a very convenient tool for comparing the S_N1 and S_N2 reaction. If you want to determine whether a substitution reaction will go by the S_N1 or the S_N2 mechanism, look first at the substrate. If the substrate is primary or methyl, the reaction will most likely be proceeded by the S_N2 mechanism. If the substrate is tertiary, the reaction will be proceeded by the S_N1 mechanism. Secondary substrates are something of a gray area; both reactions will work with these substrates, so you need to look at other features of the reaction (like the solvent) to see which mechanism may be favored over the other. With secondary alkyl substrates, you may also get a mixture of the two mechanisms.

Table 10-1 Comparing S_N1 and S_N2 Reactions

	S_N1	S_N2
Substrate	Prefers 3° over 2°	Prefers 1° over 2°
Rate equation	rate = *k*[substrate]	rate = *k*[substrate][nucleophile]
Nucleophile	Nucleophile unimportant	Requires a good nucleophile
Reaction stereochemistry	Racemic products	Inversion of configuration
Leaving groups	Good leaving group required	Good leaving group required
Solvent	Prefers polar protic solvents (alcohols, water, and so on)	Prefers polar aprotic solvents (ethers, halogenated solvents, and so on)
Rearrangements	Possible	Not possible

Seeing Elimination Reactions

Elimination reactions often compete with substitution reactions. The general form of an elimination reaction is shown in Figure 10-17. In this reaction, a substrate (typically, an alkyl halide) eliminates one equivalent (unit) of acid to make an alkene. As in substitution reactions, two possible mechanisms are available for this elimination reaction — the E1 and E2 mechanism — and both elimination reactions have similarities to their substitution counterparts.

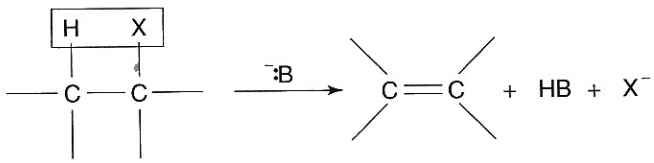
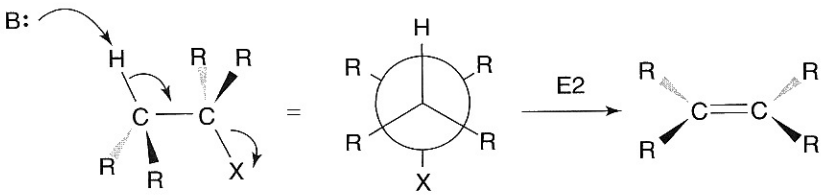


Figure 10-17: The elimination reaction.

Seeing second-order eliminations: The E2 reaction

Second-order elimination is called the E2 reaction. Like the S_N2 mechanism, the E2 mechanism takes place in a single step, as shown in Figure 10-18. A base plucks off a proton on a carbon adjacent to the leaving group, forming the double bond and giving the leaving group the boot.



Anti-periplanar geometry

Figure 10-18: The E2 elimination mechanism.

One requirement of the E2 reaction is that the hydrogen to be eliminated and the leaving group must typically be in *anti-periplanar geometry.* To be anti-periplanar means that the hydrogen and the leaving group (as well as the two carbons that will form the double bond) must be on the same plane and on opposite faces of the carbon-carbon bond, as shown in Figure 10-18.

The rate equation for an E2 reaction is as follows: rate = k[base][substrate]. Because the base is included in the rate equation, the base strength affects the rate of the reaction. The E2 reaction requires a strong base, and is the most common pathway for elimination reactions.

Seeing first-order elimination: The E1 reaction

First-order elimination, or the E1 reaction, is somewhat less common than second-order (E2) elimination. The mechanism for the E1 reaction, like the mechanism for the S_N1 reaction, has two steps, and is shown in Figure 10-19. First, the leaving group pops off to make the carbocation; this is the same first step as in the S_N1 reaction. Then, the base plucks off the hydrogen on an adjacent carbon to form the double bond.

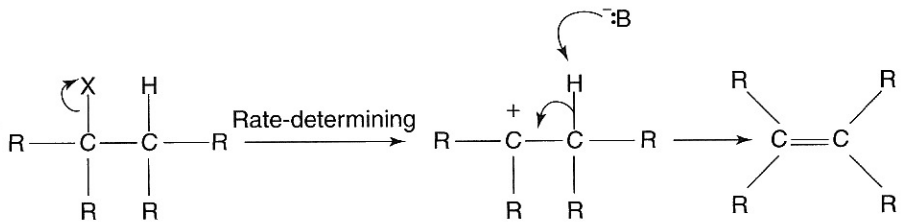


Figure 10-19: The E1 elimination mechanism.

Because the first step of the mechanism — the formation of the carbocation — is the rate-determining step, the rate follows the equation: rate = k[substrate]. Because the base is not included in the rate equation, the strength of the base is unimportant to the rate of the reaction. E2 elimination is favored with strong bases, so you see E1 elimination typically only with weak bases.

Help! Distinguishing Substitution from Elimination

Unfortunately, chemists live in an imperfect world. Reactions that are exclusively substitution or elimination are rare in the laboratory. Instead, chemists often get a mixture of the reaction products of both substitution and elimination reactions, because good nucleophiles generally are also good bases and vice-versa. Here are a few generalizations, however, that will help you distinguish which of these reactions will predominate:

- Strong bases/nucleophiles force the reaction into second-order reactions. Thus, with strong bases and nucleophiles (such as OH^-), you get S_N2 or E2 reactions, or both. With weak bases/nucleophiles, you more often get first-order products (those produced by either S_N1 or E1 reactions).
- Reactions of primary substrates generally proceed via S_N2 reactions (methyl substrates always proceed by S_N2). When very strong bases/nucleophiles are used with primary substrates, you get a mixture of both S_N2 and E2 reactions.
- Reactions of tertiary substrates produce E1 and S_N1 reactions with weak bases/nucleophiles plus a protic solvent; with strong bases, reactions of tertiary substrates produce E2 reactions.
- The reactions of secondary substrates are the hardest to predict. Under the right conditions, secondary substrates can undergo reactions by all four mechanisms. Weak bases/nucleophiles plus a protic solvent will typically give you a mixture of E1 and S_N1 products; strong bases/strong nucleophiles will typically give you a mixture of E2 and S_N2 products.
- Spotting nucleophiles that are not basic will help you distinguish substitution from elimination reactions. For example, the halides (I^-, Br^-, Cl^-) and thiols (R-SH) are nucleophilic but not terribly basic. The reactions of these molecules typically proceed exclusively by substitution. T-butoxide ($(CH_3)_3CO^-$), on the other hand, is a poor nucleophile but a powerful base, and almost exclusively forces the reaction to go via an E2 elimination.

Chapter 11

Getting Drunk on Organic Molecules: The Alcohols

In This Chapter

- Seeing and classifying alcohols
- Naming alcohols
- Comparing acidities of organic molecules
- Seeing reactions that form alcohols
- Seeing reactions that convert alcohols into other groups

When most people think of alcohol, they think of ethyl alcohol, the alcohol found in beer and wine. Many people, though, don't realize that there are many thousands of different alcohols. Ethylene glycol is an alcohol found in antifreeze; methanol is a wood alcohol that can cause blindness if ingested; isopropyl alcohol is an alcohol used for sterilizing cuts. Alcohols, like the alkenes, are an extremely important functional group, not just because they're found in so many valuable products (and not just beers and wines), but also because they're so versatile: They're easily formed and converted into many other functional groups. In this chapter, I introduce you to the alcohol functional group, show you how to name and classify alcohols, and show you reactions that both make alcohols and convert alcohols into other functional groups.

Classifying Alcohols

Alcohols are molecules that contain a hydroxyl (OH) group, and they're typically classified by the carbon to which the hydroxyl group is attached. If the carbon bonded to the OH is attached to one other alkyl group, the alcohol is classified as primary (1°); if the carbon is attached to two other alkyl groups, the alcohol is classified as secondary (2°); if the carbon is attached to three alkyl groups, the alcohol is classified as tertiary (3°, see Figure 11-1).

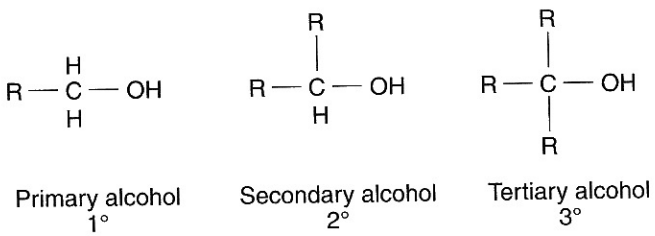


Figure 11-1: Alcohol classification.

An Alcohol By Any Other Name: Naming Alcohols

You can name alcohols by just extending the nomenclature rules used for alkanes (refer to Chapter 7 for an alkane refresher). To name an alcohol you follow these five steps:

1. **Determine the parent name of the alcohol by looking for the longest chain that includes the alcohol.**

 Snip the *e* off of the suffix for the alkane and replace it with the suffix *-ol,* which stands for alcoh*ol.* For example, a two-carbon alcohol would not be ethane but ethanol.

2. **Number the parent chain. Start numbering from the side closest to the hydroxyl group.**
3. **Identify all of the substituents off of the parent chain and name them.**
4. **Order the substituents alphabetically in front of the parent name.**
5. **Identify the location of the hydroxyl group by placing a number in front of the parent name.**

Now try naming the alcohol shown in Figure 11-2.

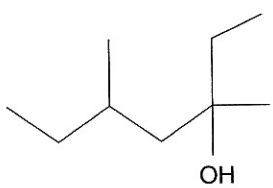


Figure 11-2: An alcohol.

First, find the parent chain, as shown in Figure 11-3. The parent chain is the longest chain of carbons that contains the hydroxyl group. In this case, the parent chain is seven carbons long, so this is a heptanol.

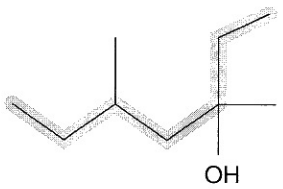


Figure 11-3: The parent group.

Then number the parent chain, starting from the end that reaches the hydroxyl group the soonest. In this case, that's from right to left. (See Figure 11-4.)

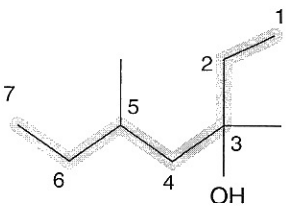


Figure 11-4: Numbering the chain.

Find and name the substituents. The molecule shown in Figure 11-5, has two methyl group substituents — one at the number-three carbon and one at the number-five carbon.

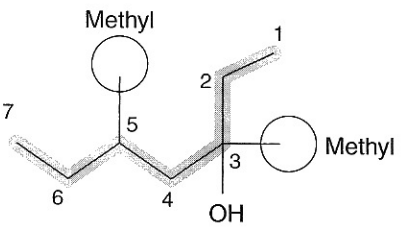


Figure 11-5: Identifying substituents.

Then place the substituents (in alphabetical order) in front of the parent group. Indicate the position of the hydroxyl group by placing a number in front of the parent name. The two methyl groups combine to make dimethyl, and the name for this alcohol is therefore 3,5-dimethyl-3-heptanol.

Alcohol-Making Reactions

So now take a look at how you can make alcohols.

Adding water across double bonds

Chapter 8 shows you two reactions that produce alcohols from alkenes. The oxymercuration of alkenes makes the Markovnikov alcohol (the alcohol with the OH on the most highly substituted carbon) while hydroboration makes the anti-Markovnikov alcohol (the alcohol with the OH on the least-substituted carbon). This conversion is outlined in Figure 11-6.

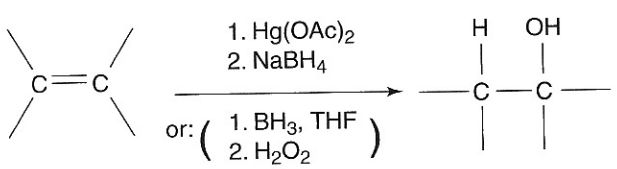
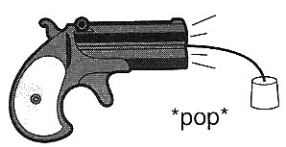
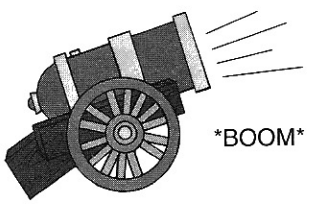


Figure 11-6: Adding water to an alkene.

Reduction of carbonyl compounds



$NaBH_4$
Mild reducing agent

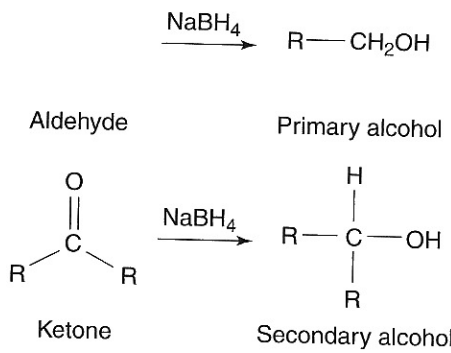


$LiAlH_4$
Strong reducing agent

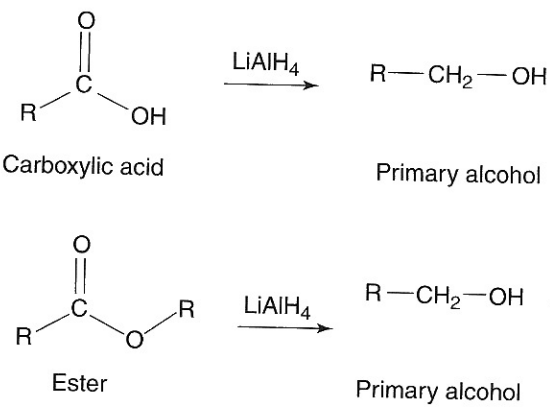
Figure 11-7: The relative strengths of reducing agents.

What do I mean by that? Well, sodium borohydride can reduce carbonyl compounds that are easy to reduce to alcohols, like aldehydes and ketones. But this reagent is not strong enough to reduce the more stubborn carbonyl compounds like esters and carboxylic acids. For that job, you bring out the cannon reagent (lithium aluminum hydride), which is strong enough for the task.

Reducing aldehydes with sodium borohydride (or lithium aluminum hydride) is a very convenient way of making primary alcohols, as shown in Figure 11-8. Similarly, the reduction of ketones with sodium borohydride is a convenient way of preparing secondary alcohols. Tertiary alcohols cannot be prepared by reduction.



Lithium aluminum hydride is strong enough to reduce both carboxylic acids and esters, as shown in Figure 11-9. Both carboxylic acids and esters are reduced to primary alcohols with this reagent.



cohol

aluminum hydride reduction.

The Grignard reaction

Another extremely useful reaction for making alcohols is the Grignard reaction (pronounced GRING-guard). To make alcohols using the Grignard reaction, you react a "Grignard reagent" with a carbonyl compound. Making a Grignard reagent is fairly simple: You simply add magnesium to an alkyl halide, as shown in Figure 11-10, which inserts the magnesium into the C-X bond to make the Grignard reagent.

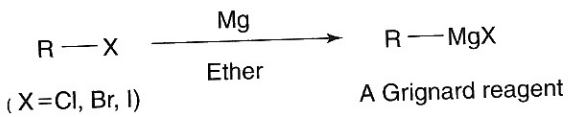


Figure 11-10: Making a Grignard reagent.

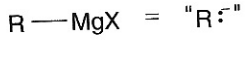


Figure 11-11: A Grignard reagent.

in Figure 11-12.

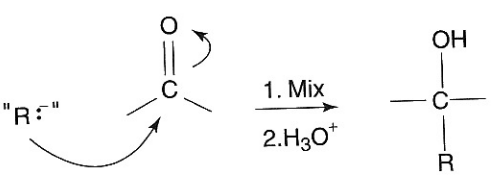
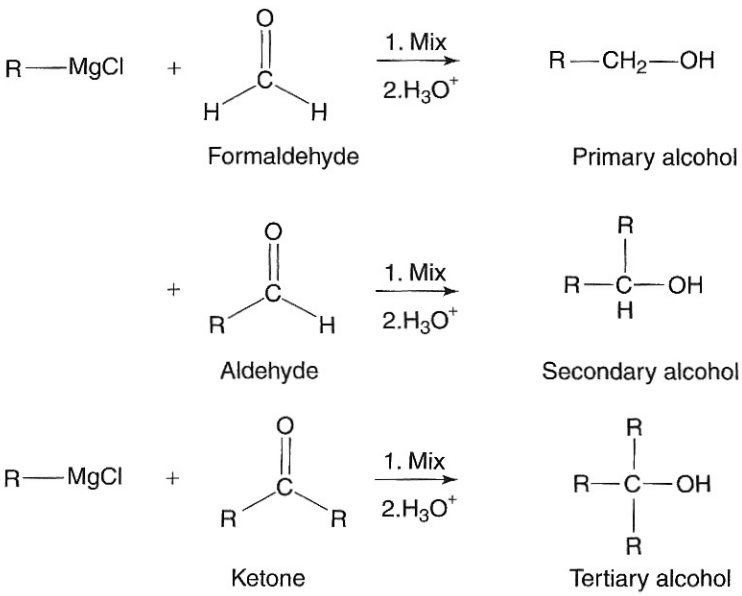


Figure 11-12: The Grignard reaction.

Although you can only make primary and secondary alcohols by reduction, you can make all kinds of alcohols using the Grignard reaction. If you react a Grignard reagent with formaldehyde as shown in Figure 11-13, you can make primary alcohols. If you react it with an aldehyde, you get secondary alcohols. If you react it with ketones, you get tertiary alcohols.



of Alcohols

So what can you do with alcohols? Now that you've seen reactions that make alcohols, I show you reactions that convert alcohols into other functional groups.

Losing water: Dehydration

One of the best reagents for converting alcohols into alkenes is phosphorous oxychloride ($POCl_3$). This reagent causes the alcohol to lose water to make the alkene, as shown in Figure 11-14.

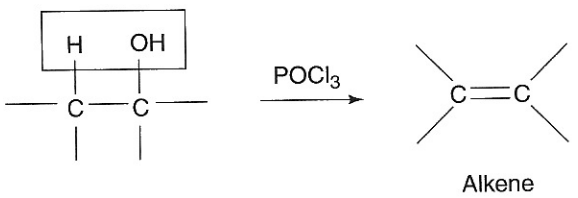


Figure 11-14: The dehydration of an alcohol.

Making ethers: Williamson ether synthesis

Ethers can also be made from alcohols. Reacting an alcohol with sodium metal forms an alcoxide, the alcohol's conjugate base, as shown in Figure 11-15. Alcoxides are strong nucleophiles that can react with primary halides to make ethers in an S_N2 reaction (refer to Chapter 10).

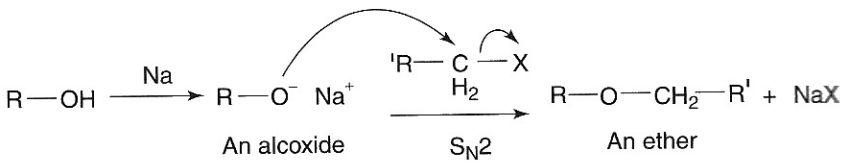
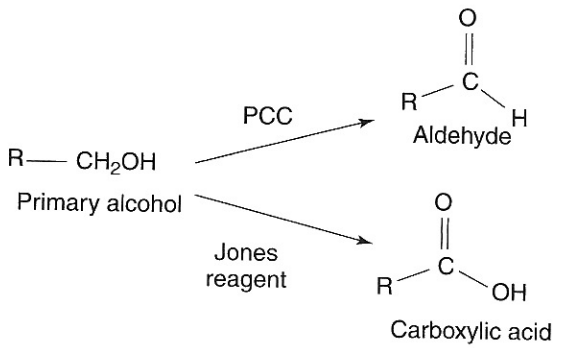
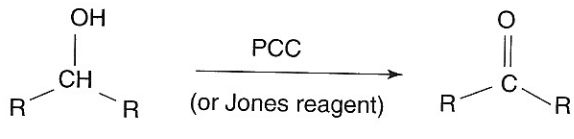


Figure 11-15: The Williamson ether synthesis.

Oxidation of alcohols

You cannot oxidize a tertiary alcohol.


O
C
R
H
Aldehyde
PCC
R— CH_2OH
Primary alcohol
Jones
reagent
O
C
R
OH
Carboxylic acid


OH
CH
R
R
PCC
(or Jones reagent)
O
C
R
R
Ketone

alcohols.

Chapter 12

Side-By-Side: Conjugated Alkenes and the Diels-Alder Reaction

In This Chapter

- Seeing the difference between conjugated and isolated alkenes
- Examining 1,2- and 1,4-additions to alkenes
- Distinguishing kinetics from thermodynamics
- Seeing the Diels-Alder reaction of conjugated dienes

Some of the first reactions that you saw in organic chemistry were likely the reactions of alkenes (discussed in Chapter 8), but those reactions don't close the book on this important functional group. Multiple double bonds that alternate in a carbon chain, called *conjugated alkenes,* have different properties and reactivities than double bonds that exist all by their lonesome. In this chapter, I explore some of these differences, and use the reaction of conjugated double bonds with acids to explain the difference between kinetics and thermodynamics. I also show you perhaps the most interesting reaction in organic chemistry, the Diels-Alder reaction, which lets you easily form rings and bizarre bicyclic structures.

Seeing Conjugated Double Bonds

Conjugated double bonds are molecules in which two or more double bonds are separated by one carbon-carbon single bond, as shown in Figure 12-1. The double bonds are alternating, in other words. Isolated double bonds are those that are separated by more than one carbon-carbon single bond.



Figure 12-1: Conjugated versus isolated alkenes.

One feature of conjugated alkenes is that they're more stable than isolated alkenes. You can justify this added stability by writing out the resonance structures for a conjugated alkene (see Chapter 3 for more on resonance structures) and recalling that resonance is a stabilizing feature of molecules. Figure 12-2 shows the resonance structures for the conjugated diene butadiene. In contrast, isolated double bonds have no resonance structures and so are less stable.

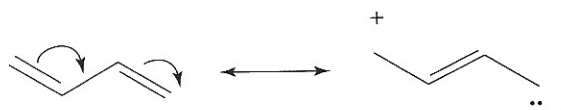


Figure 12-2: One resonance structure for butadiene.

Addition of Hydrohalic Acids to Conjugated Alkenes

In addition to their greater stability over isolated double bonds, conjugated double bonds react differently than isolated double bonds. The addition of hydrohalic acids (like HBr, HCl, and so forth) to double bonds is shown in detail in Chapter 8. But hydrohalic acids react somewhat differently with conjugated double bonds than they do with isolated double bonds.

You can see how this difference in reactivity comes about by looking at the mechanism for this reaction, shown in Figure 12-3. The first step in the mechanism is the protonation of one of the double bonds to form the carbocation. (Note that in general the cation prefers to be secondary rather than primary; see Chapter 8 for more on carbocations.) This cation has two resonance structures, one in which the positive charge resides on the number two carbon and one in which the positive charge resides on the number four carbon. Thus, the true structure of the cation lies somewhere in between these two resonance

structures, with a molecule that has some positive charge located on the number two carbon and some positive charge on the number four carbon. The halide can attack either of these two positively charged spots. Attacking the number two carbon leads to the 1,2-addition product (because the hydrogen has added to position one and the halide to position two), while attacking at the number four carbon leads to the 1,4-addition product (because the hydrogen has added to position one and the halide to position four).

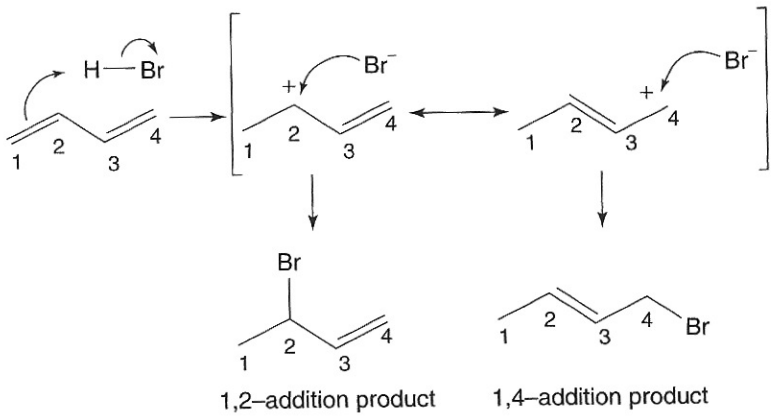


Figure 12-3: Mechanism of 1,2-addition and 1,4-addition.

Reaction temperature:	0°C	70%	30%
	40°C	15%	85%

Seeing the reaction diagram of conjugate addition

So, which of the two conjugate addition products will be favored? Interestingly, the relative amount of each material produced depends on the temperature of the reaction. While you get mostly 1,2-addition at lower temperatures (at 0°C), you get mostly 1,4-addition at higher temperatures (at 40°C). To see why this is the case, you need to look at the reaction diagram for the two different pathways, shown in Figure 12-4. Note that a reaction diagram plots the progress of the reaction versus the energy of the reaction (refer to Chapter 10 for more on reaction diagrams).

Both pathways are initially identical because both go through the same carbocation. Then the pathways diverge. You can see from the reaction diagram that the 1,2-addition product has a lower energy of activation for the second

step (a smaller energy hill to climb), but gives a higher-energy product, while the 1,4-addition reaction pathway has a higher energy of activation for the second step, but leads to a more stable, lower-energy product.

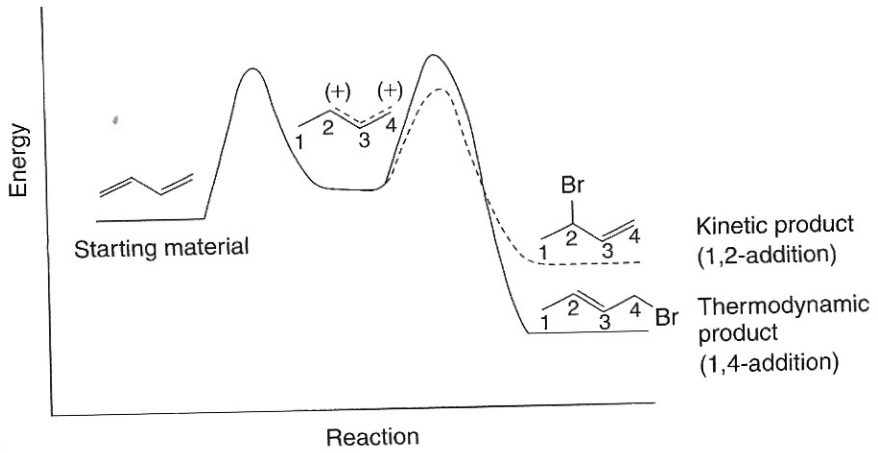


Figure 12-4: Reaction diagram for conjugate addition.

At low temperatures, the reaction supplies enough energy for the reaction to go over the smaller barrier to reach the 1,2-addition product, but not enough energy to go over the higher-energy barrier to reach the 1,4-addition product. Because at low temperatures the reaction is irreversible — that is, after the reaction has gone over the energy hill to make product, the reaction doesn't have enough energy to climb the higher hill back to the cation intermediate — after the starting material is converted to product, it stays as product and doesn't go back to the intermediate carbocation. In this way, at low temperatures you favor the 1,2-addition product that has the lower activation barrier, even though it results in a higher-energy product. The product formed with the lowest activation barrier is called the *kinetic product* using organic-speak.

At higher temperatures (around 40°C), the reaction is reversible (has enough energy to return to the cation after it's made the kinetic product) and can reach equilibrium. Any system at equilibrium will favor the lower-energy product, called the *thermodynamic product.* The reaction at high temperature has enough energy to go over the higher-energy activation barrier to reach the more stable product. Additionally, because enough heat is present to make the 1,2-addition reaction reversible, eventually most of the 1,2-product will go back up the hill to the carbocation state. Once there, the reaction will eventually lead to 1,4-addition, because this reaction gives the lower energy product.

Comparing kinetics and thermodynamics of conjugate addition

Kinetics and thermodynamics are easy to confuse, but here's how you can remember the difference between the two. Kinetics refers to the rates of reactions. Reaction rates depend on the heights of the energy barriers in a reaction (the activation energies). Thermodynamics, on the other hand, refers to the relative energies of the starting material and the product (the change in energy). If you want a reaction to be under kinetic control, you run the reaction at low temperature so that only low energy hills will be climbed by the reaction, and the kinetic product will be favored. At higher temperatures, when a reaction is at equilibrium, the reaction is under thermodynamic control, and the lowest-energy product is favored, regardless of the height of the activation barrier.



In general, 1,2-addition typically leads to the kinetic product, while 1,4-addition leads to the thermodynamic product (refer to Figure 12-4 for the specific case of the HBr addition to butadiene). So to get the 1,2-addition product on a conjugated alkene you typically run the reaction at lower temperature, while to get the 1,4-addition product you run the reaction at higher temperatures.

The Diels-Alder Reaction

One of the most interesting differences between isolated alkenes and conjugated alkenes is that conjugated alkenes can undergo the Diels-Alder reaction. The Diels-Alder reaction is probably the funkiest reaction you encounter in organic chemistry. It's also one of the most valuable reactions in organic chemistry, because in a single step this reaction produces two valuable carbon-carbon bonds (so valuable to chemists that the discoverers, Otto Diels and Kurt Alder, shared the Nobel Prize in chemistry for discovering this reaction). The reaction is extremely useful in the construction of six-membered rings and bicyclic molecules.

The general form of the Diels-Alder reaction is shown in Figure 12-5. In this reaction, a conjugated diene reacts with an alkene (called the *dienophile,* or diene lover) to form a six-membered ring. The reaction occurs in a single step; it produces no intermediates. As shown in the mechanism drawing, the three double bonds in the two starting materials are used to make two new carbon-carbon single bonds and one new carbon-carbon double bond in the product.

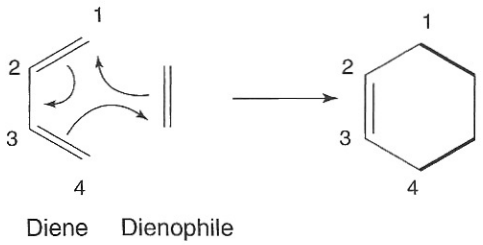


Figure 12-5: The mechanism of the Diels-Alder reaction.

Seeing the diene and the dienophile

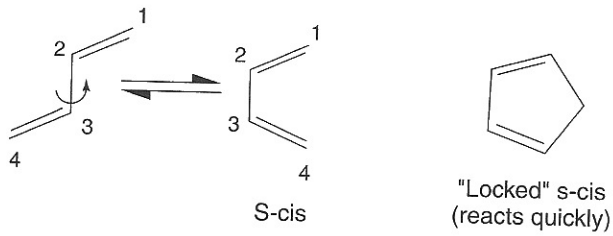
The Diels-Alder reaction prefers certain dienes and dienophiles. Dienes that are substituted with electron-donating groups react faster than those that are unsubstituted. Conversely, dienophiles react the fastest when they're substituted with electron-withdrawing groups.

Good electron-donating groups (abbreviated EDG) to put on dienes for the Diels-Alder reaction include ethers (OR), alcohols (OH), and amines (NR_2). Good electron-withdrawing groups (abbreviated EWG) for the dienophile include cyano groups (CN), nitro groups (NO_2), and all of the carbonyl compounds (including esters, aldehydes, acids, ketones, and so on). These groups are shown in Figure 12-6.



Figure 12-6: Some diene and dienophile preferences.

Another requirement of the diene is that it be in the s-cis conformation so that the two double bonds are in the proper orientation to undergo the reaction. The *s-cis conformation* is the one in which both of the double bonds are on the same side of the carbon-carbon single bond that separates the two double bonds, as shown in Figure 12-7. Dienes in rings react very quickly in the Diels-Alder reaction because they're locked in the s-cis conformation.



Stereochemistry of addition

One of the most valuable features of the Diels-Alder reaction is that the reaction is *stereoselective* — that is, it preferentially forms one stereoisomer over another. (For a discussion of stereochemistry, check out Chapter 6.) With a disubstituted dienophile, if the two substituents on the dienophile start *cis*, they end up *cis* in the product; if they start *trans*, they end up *trans* in the product, as shown in Figure 12-8.

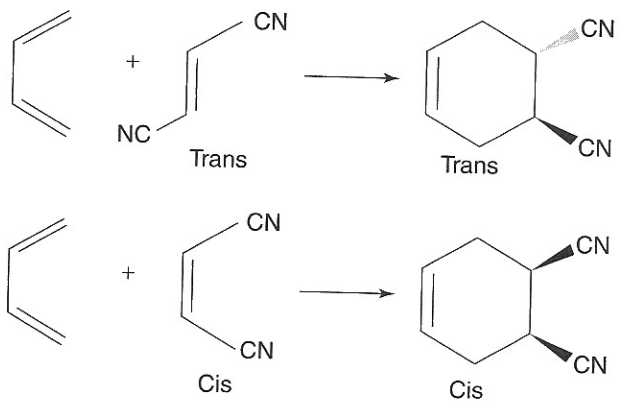


Figure 12-8: Stereochemistry of addition in a Diels-Alder reaction.

Seeing bicyclic products

If the diene is in a ring, you get bicyclic products from the Diels-Alder reaction, as shown in Figure 12-9. And if the two substituents on the dienophile are cis, the two stereoisomers could end up going down relative to the carbon bridge in the product, called *endo addition,* or sticking up toward the carbon bridge, called *exo addition.* The Diels-Alder reaction preferentially forms the endo product.

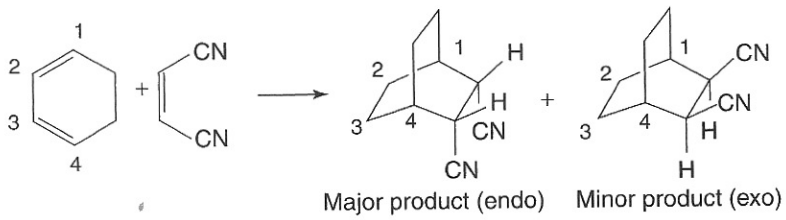


Figure 12-9: The endo and exo products of a Diels-Alder reaction.

Problem-Solving: Determining Products of Diels-Alder Reaction

Diels-Alder reactions can look confusing, but following these four simple steps will help you to determine the products of these reactions.

1. **Orient the diene and the dienophile correctly.**

 In this step, you make sure that the double bonds are oriented correctly (the diene double bonds are pointing in the direction of the dienophile), and that the diene is in the s-cis conformation (if it isn't, you need to rotate it so that it is).

2. **Number the diene carbons (1 through 4).**

 You can start the numbering on either end of the diene. The numbering is just a way for you to keep track of where bonds should be formed to make the product.

3. **Work the reaction.**

 Make a bond from the number-one carbon on the diene to one side of the dienophile. Then make a bond from the number-four carbon to the other side of the dienophile. Get rid of the two double bonds in the starting material between carbons 1 and 2 and 3 and 4, and put a double bond between carbon 2 and 3 in the product.

4. **Make sure you have the correct stereochemistry.**

 If you start with a cis disubstituted dienophile the product should be substituted cis; if the dienophile starts trans, it should end up trans. With bicyclo products, make sure that you show endo stereochemistry in the product.

Now try taking the problem shown in Figure 12-10 through the four steps.

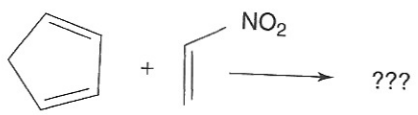


Figure 12-10: A Diels-Alder reaction.

Step 1: Orienting the molecule

Start by orienting the diene so that the two double bonds in the diene point in the direction of the dienophile (with the single bond that connects the double bonds oriented away from the dienophile). In this case, you need to rotate the diene 180°, as shown in Figure 12-11. Because this diene is in a ring, you don't have to worry about twisting the diene to the s-cis conformation because dienes in rings are locked in the s-cis conformation.

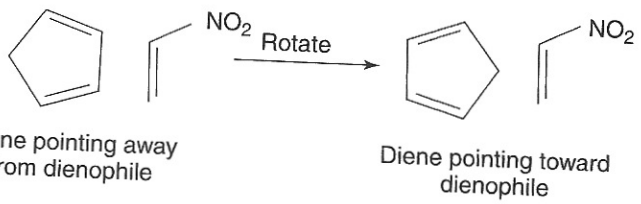


Figure 12-11: Orienting the diene.

Step 2: Numbering the diene

Next, number the carbons on the diene (1 through 4). Start the numbering on any side of the diene. In Figure 12-12, the numbering begins on the top.

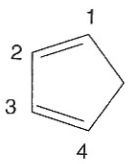


Figure 12-12: Diene numbering.

Step 3: Making the bonds

Now that everything's lined up, take a deep breath and work the reaction. You make bonds between the number one carbon on the diene and the dienophile, and between the number four carbon and the dienophile. You end with a double bond between carbons two and three. Notice that in the reaction is shown in Figure 12-13, the fifth carbon in the diene ring is flipped up, forming a pointed "bridge" between carbons one and four.

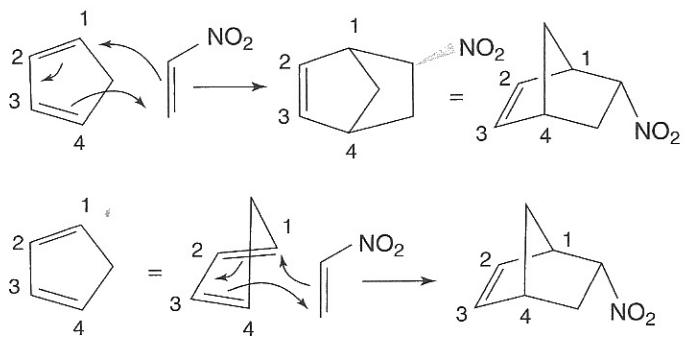


Figure 12-13: Two different ways of visualizing this Diels-Alder reaction.

Chapter 13

Lord of the Rings: Aromatic Compounds

According to organic legend, the structure of the parent aromatic system, benzene, came to the chemist August Kekulé in a dream. For a long time the structure of benzene — a liquid isolated from a tarry residue from burning petroleum gas — had eluded chemists, and many structures for the compound had been proposed by big names in the field. Kekulé claimed that in a dream he saw a snake devouring its own tail, forming a circle. Benzene must be a ring, he thought when he awoke, and jotted down the correct structure of the compound (or so he claimed, somewhat dubiously, many years later). Kekulé's intuition about the cyclic structure of benzene was correct, and soon led to the discovery of aromatic rings other than benzene.

Benzene and other *aromatics* are a highly interesting class of ringed compounds of exceptional stability. In this chapter, I show you how to name aromatics, and discuss aromatic compounds other than benzene that have properties and reactivities similar to those of benzene. I show you how to determine whether a ring system is aromatic, show you what makes aromatic compounds so stable, and cover the reactions of benzene.

Defining Aromatic Compounds

Aromatics are a class of ring compounds containing double bonds. The name *aromatic* comes from the fact that many of the aromatic compounds that were first isolated were highly fragrant; the lovely odors of such substances as vanilla, almonds, and wintergreen are due to the presence of aromatic compounds in these products. But many aromatic compounds are unpleasant smelling, or have no odor at all. Most simple aromatics, in fact, are obtained commercially from coal tar. Aromatic compounds contain double bonds, but they don't react like alkenes, and so are classified as a separate functional group. Benzene, for example, doesn't behave as if it were 1,3,5-cyclohexatriene. While bromine reacts rapidly with alkenes to make dibromides (see Figure 13-1), bromine is completely unreactive with benzene. This lack of reactivity results from aromatics being much more stable than alkenes.

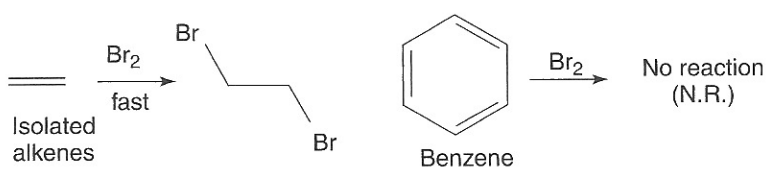


Figure 13-1: The relative stability of an alkene and benzene in the presence of bromine.

Because of this greater stability, aromatic compounds require significantly more vigorous reaction conditions to make them react compared to the conditions required to react simple alkenes. Aromatic rings scoff when exposed to the relatively mild reagents that react with alkenes (reagents such as those used in hydroboration, oxymercuration, and HBr addition, which are shown in Chapter 8). Trying to react aromatics with these reagents is like shooting popguns at a well-defended castle. These reagents simply glance off the rings, and remain impotent in the reaction flask. You need to unleash the howitzer reagents to get aromatic rings to react, and I show you these later in the chapter.

Structure of benzene

The actual structure of benzene is the hybrid of its two resonance structures shown in Figure 13-2. (For a review of resonance structures, see Chapter 2.)

Every bond in benzene is exactly the same length — neither as long as a single bond nor as short as a double bond — and its bond character can best be described as being 1.5, the length between a single and double bond.

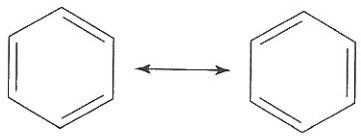


Figure 13-2: Benzene resonance structures.

Because benzene is a hybrid of two resonance structures, to more accurately show the location of the pi electrons with a single structure, all of the double-bond electrons are often represented with a circle (as shown in Figure 13-3) rather than with individual double bonds. This circle drawing of benzene more accurately depicts the electron distribution of benzene because it shows all atoms and bonds as equal. But, because the number of pi electrons is unclear in these drawings (and because reactions are better shown from the double-bond containing structures), I avoid using this circle representation for benzene in this book. Just keep in mind that when the double-bond containing structures for benzene are drawn, these hybrid structures are assumed.

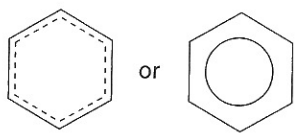


Figure 13-3: Benzene.

Diversity of aromatic compounds

Although benzene is the parent aromatic compound, many other aromatic compounds that have the same exceptional stability as benzene are known. Some of these aromatics consist of benzene rings smooshed together to make fused rings, such as benzopyrene (Figure 13-4). These fused aromatic compounds, which are found in coal, have been found to be toxic. Chimney sweeps and other workers exposed to these compounds for long periods run the risk of developing cancers because of exposure to the benzopyrene and other aromatic compounds found in chimney soot.

Aromatic compounds come in rings of all sizes, and many include heteroatoms like oxygen, nitrogen, and sulfur; aromatics that contain such heteroatoms

include furan and pyridine, shown in Figure 13-4. All of the DNA bases, including adenine, which is also shown in Figure 13-4, have aromatic character. Because they're so stable, aromatic compounds are ubiquitous in nature.

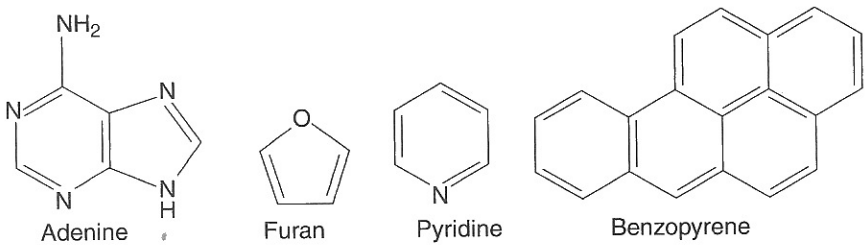


Figure 13-4: Some aromatic rings found in nature.

So what exactly makes a molecule aromatic?

At first, many chemists thought that all rings that contained alternating double bonds all the way around a ring would have the same aromatic character as benzene — and the same exceptional stability that comes along with this structure. This assumption is not correct, however. Cyclobutadiene, for example, shown in Figure 13-5, is an extremely unstable compound, and rapidly *dimerizes* (reacts with another molecule of cyclobutadiene) in solution (via the Diels-Alder reaction from Chapter 12; you get brownie points if you can draw the product!). While benzene, as a result of its aromaticity, is more stable than its open chain analog, 1,3,5-hexatriene, cyclobutadiene is actually less stable than its open-chain counterpart, 1,3-butadiene. Therefore, some rings are stabilized by these double-bond containing rings and become aromatic, while others (like cyclobutadiene) are destabilized and become what are called *anti-aromatic* rings.

Hückel's 4n + 2 rule

A chemist named Erich Hückel explained this somewhat confusing result. He observed that planar ring systems that contained $4n + 2$ pi electrons (where n is an integer), were stabilized and aromatic, while ring systems with $4n$ pi electrons were destabilized and anti-aromatic. Thus, benzene, with its six pi electrons (two pi electrons from each double bond) is aromatic because it follows the $4n + 2$ rule, where $n = 1$. Cyclobutadiene, on the other hand, is anti-aromatic because of its four pi electrons; it follows the $4n$ equation, where $n = 1$.

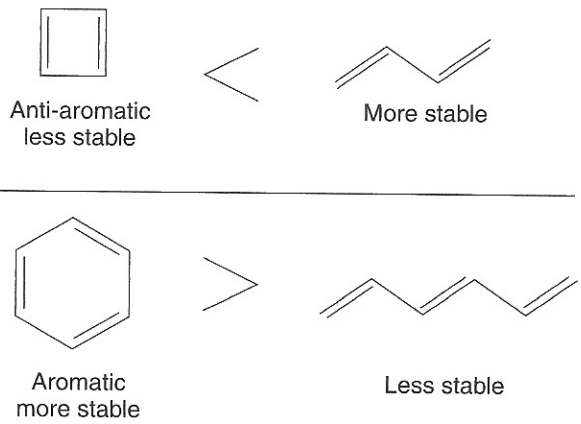


Figure 13-5: The relative stabilities of some ringed and open-chain alkenes.

Hückel's equation, useful as it is, doesn't explain why the rings that contain a *Hückel number of pi electrons* ($4n + 2$) have this stabilizing feature of aromaticity, while those with a *non-Hückel number* ($4n$) are destabilized. Although you know that benzene has resonance structures, and that resonance structures generally contribute to a molecule's stability, the best explanation for the stability of aromatic compounds comes from molecular orbital theory, which is covered in the next section.

Explaining Aromaticity: Molecular Orbital Theory

Molecular orbital (MO) theory offers a more sophisticated model of bonding than the valence bond model (that is represented with Lewis structures). Of course, this greater sophistication comes at a cost: Molecular orbital theory is not nearly as user-friendly as the valence bond model. It's been whispered (and not only among students) that while valence bond theory is too good to be true, MO theory is too true to be good. That description is somewhat unfair to both models, but it's true that organic chemists have staved off using MO theory even when an MO model gives the correct description of a molecule and the valence bond model is wrong. For example, organic chemists prefer to use resonance structures to correct flaws in the valence model's depiction of pi and nonbonding electrons rather than switch to the more precise (but more unwieldy) MO theory.

What the heck is molecular orbital theory?

In valence bond theory, electrons are located in bonds between atoms or as nonbonding electrons on an atom. In molecular orbital theory, electrons are not restricted to being localized between two atoms or on an atom itself. Instead, the electrons are allowed to spread across the entire molecule. If you think of orbitals as being like apartments for electrons, the electron has just been allowed to move from the small, cloistered hovel of valence bond theory into the much more spacious suite of molecular orbital theory. Because electrons can delocalize across the entire molecule in MO theory, the orbitals that these electrons reside in are called *molecular orbitals,* abbreviated Ψ (psi, pronounced "sigh," as in, "Sigh! Why do I have to deal with molecular orbital theory?").



Valence bond theory and molecular orbital theory are just models for depicting the actual location of electrons in a molecule. While valence bond theory is the most user friendly of the two, it's not as accurate as MO theory because it doesn't do as good a job at modeling how electrons can spread out over an entire molecule in certain instances (like in aromatic rings).

Making MO diagrams

A very informative orbital schematic is called a molecular orbital diagram. A *molecular orbital diagram* shows the number and relative energies of the different molecular orbitals for a molecule, and the electron occupancy in each of these orbitals. These diagrams are just like the atomic electron configurations you drew in introductory chemistry (reviewed in Chapter 2), except that these diagrams are for molecules instead of atoms, and in these diagrams you fill molecular orbitals rather than atomic orbitals.

To make an MO diagram, you need to follow three guidelines:

- Molecular orbitals are made by combining atomic orbitals (like *s and p* orbitals). The number of atomic orbitals combined must equal the number of molecular orbitals in the molecule. If you put six atomic orbitals in, for example, you must get six molecular orbitals out.
- The MOs that go down in energy are called bonding molecular orbitals; the MOs that go up in energy are called antibonding molecular orbitals.
- Electrons fill molecular orbitals in the same way that electrons fill atomic orbitals in an atom — that is, the lowest energy orbitals fill first with a maximum of two electrons per orbital, following Hund's rule. (See Chapter 2 for a review of atomic orbitals and Hund's rule.)

Every carbon atom in benzene is sp^2 hybridized. Therefore, every carbon atom in benzene has one *p* orbital orthogonal (at a right angle) to the plane of the benzene ring, as shown in Figure 13-6. The pi orbitals in benzene are made from the overlap of these *p* orbitals. When making these MO diagrams for benzene and other aromatics, you usually only care about the pi orbitals (because only the pi electrons contribute to aromaticity). So, on these MO diagrams you leave out all of the sigma molecular orbitals, and combine just the *p* orbitals to make your pi molecular orbitals (recall that only *p* orbitals make pi bonds).

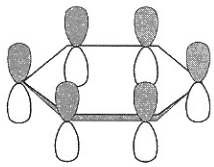


Figure 13-6: Benzene *p* orbitals.

Two rings diverged in a wood: Frost circles

Because benzene has six *p* orbitals (one from each carbon), exactly six pi molecular orbitals must be formed from these six orbitals following the first guideline. A very handy guide to making the molecular orbital diagrams for these ring systems is a Frost circle. A *Frost circle* enables you to quickly place the six orbitals on the molecular orbital diagram, and gives you the relative energies of the orbitals.

Making a Frost circle is easy: You simply draw a circle, and within the circle draw the carbon ring with one of its corners pointing down. Each point where the ring touches the circle is the location of one of the molecular orbitals. After you have all of the orbitals situated at the correct energy level, you fill the orbitals with the number of pi electrons in the ring, and — *voilà!* — you have the molecular orbital diagram.

After drawing a couple of these molecular orbital diagrams for ring systems, you notice that in many diagrams two orbitals are at the same energy level. Such orbitals are called *degenerate orbitals,* using organic-speak.

Making the MO diagram of benzene

The construction of the molecular orbital diagram of benzene is shown in Figure 13-7. First, a circle is drawn, and then a six-membered ring is plopped inside the circle with the point down.



One of the most common mistakes in constructing MO diagrams using a Frost circle is to forget to put the point of the ring *down* in the circle.

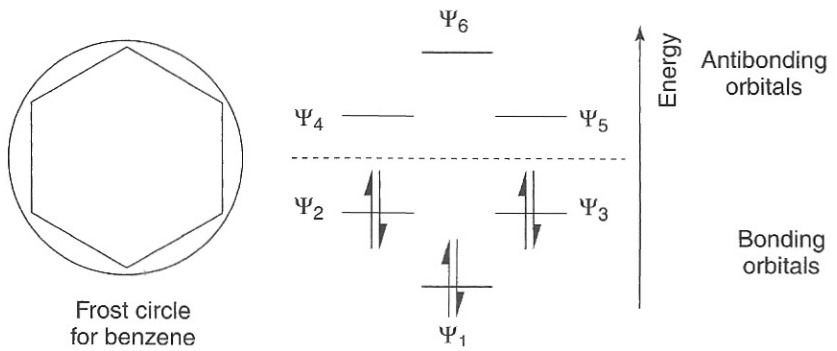


Figure 13-7: The Frost circle and the molecular orbital diagram of benzene.

Every point where the six-membered ring touches the circle represents the location of one of the molecular orbitals (which I have transposed to the right of the circle in the figure for clarity). The orbitals lower than the center of the circle are called *bonding orbitals,* while those higher than the center of the circle are called *antibonding orbitals.* Bonding orbitals are lower in energy than antibonding orbitals. Because benzene has six pi electrons, you fill the lowest energy orbital (Ψ_1) plus the two degenerate orbitals above it (Ψ_2 and Ψ_3). Note how lovely the electronic structure of benzene is — all three of these low-energy bonding orbitals are completely filled with electrons, while each of the high-energy antibonding orbitals remains empty. Because each of the filled orbitals in benzene is low in energy, benzene is exceptionally stable.

Seeing the MOs of benzene

Of course, these MO diagrams don't tell you what the individual molecular orbitals look like. Each molecular orbital in benzene is made from a combination of the six atomic *p* orbitals. Recall that *p* orbitals have a node — a region of zero electron density at the center of the orbital where the wave function that describes the orbital changes sign. (This change in sign is made apparent by shading one half of the *p* orbital.) For a bonding interaction to occur between two *p* orbitals, the orbitals must line up so that each lobe that overlaps with another p orbital has the same sign. When orbitals line up with an opposite sign, it creates an antibonding (high-energy) interaction and a node (a region of zero electron density) between the orbitals. An example for the overlap of *p* orbitals is shown in Figure 13-8.

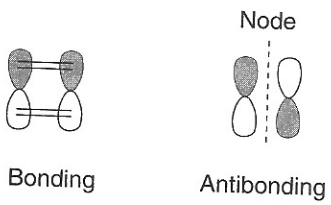


Figure 13-8: Bonding and antibonding *p* orbitals.

The MOs of benzene are shown in Figure 13-9. When all of the *p* orbitals circle the benzene such that all the signs match up, every single orbital overlaps with the other in a bonding interaction and makes the molecular orbital (Ψ_1) with the lowest possible energy. When one side of the ring has orbitals that line up one way, and the other side has orbitals that line up the opposite way, a molecular orbital is created that has one node across the benzene ring. The molecular orbitals Ψ_2 and Ψ_3 each have one node. A general feature of pi molecular orbitals is that the lowest energy level orbitals have zero nodes, the second energy level has one node, the third has two nodes, and so on. The more nodes a molecular orbital contains, the higher the energy of the orbital. In the highest energy molecular orbital of benzene (Ψ_6), every *p* orbital is antibonding with its neighboring orbital.

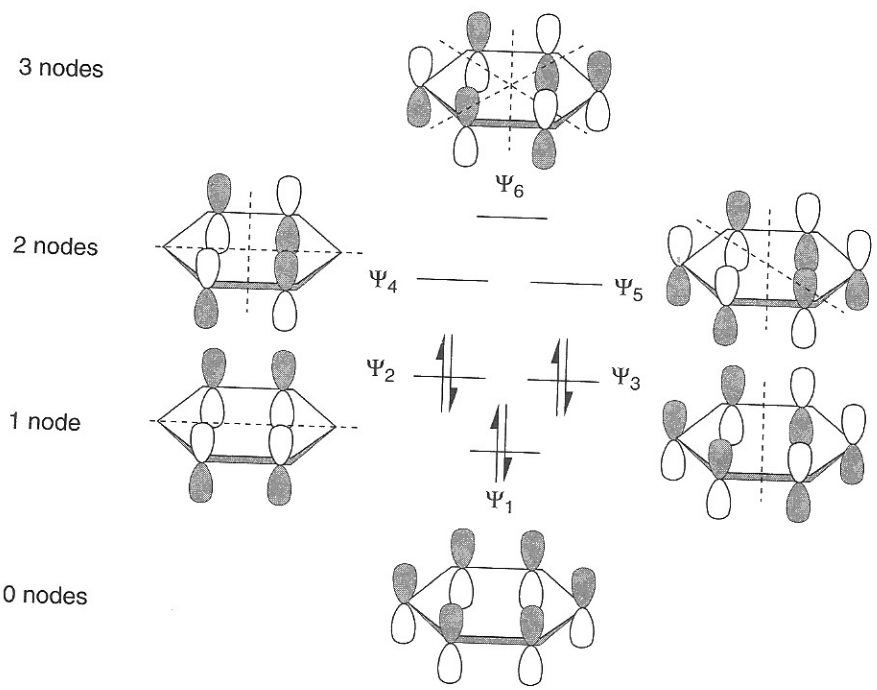


Figure 13-9: The molecular orbitals of benzene.

You might wonder how an electron is able to hop across nodes, those regions of zero electron density where electrons are not allowed. Continuing the apartment analogy, these nodes are like having rooms in your apartment, but no doorways. How do you get from one room into the next? The confusion comes from thinking of electrons only as particles, like little planets orbiting the nucleus sun, and ignoring the wave properties of electrons. Here a wave analogy is useful. When you thumb a guitar string on the fret of the guitar and then pluck the string, you see the vibration propagate past your thumb, a place where the vibration is zero. In the same way, an electron, because it can behave as a wave, can hop past the nodes in a molecular orbital. When thinking of node-hopping, think of the electron as a wave rather than as a particle.

Making the MO diagram of cyclobutadiene

Now try making the MO diagram for cyclobutadiene, which is unstable and anti-aromatic (see Figure 13-10). You make the Frost circle the same as you did with benzene, except that you plunk a four-membered ring point down in the circle to obtain the MO levels. (Note that you get four molecular orbitals, because you start with four *p* atomic orbitals.) Because cyclobutadiene has four pi electrons (again, two from each double bond), you completely fill the first molecular orbital (Ψ_1). The next two electrons are placed in the Ψ_2 and Ψ_3 orbitals, which are degenerate. According to Hund's rule (refer to Chapter 2), you must place one electron into each degenerate orbital rather than pairing them in the same orbital. Thus, unlike benzene, in which all bonding orbitals are filled with electrons, two orbitals in cyclobutadiene are only partially filled. Cyclobutadiene, therefore, is essentially a *diradical* (a species containing two unpaired electrons)! Certainly, you wouldn't have guessed that from looking at the misleading Lewis structure.

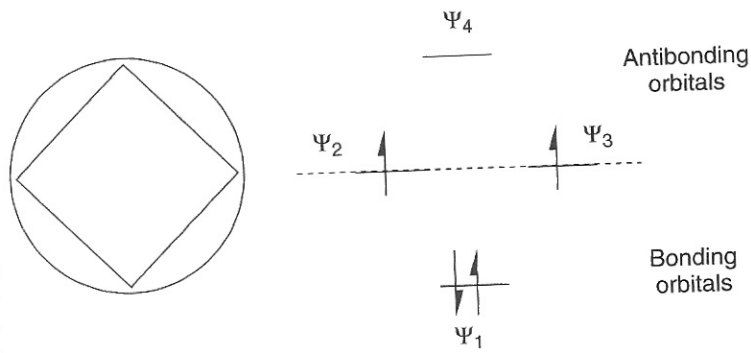


Figure 13-10: The Frost circle and the molecular orbital diagram of cyclobutadiene.

In fact, you see that this trend is followed for all aromatic and anti-aromatic rings. Aromatic rings have only filled bonding orbitals, while anti-aromatic rings have two unfilled orbitals, making them extremely grouchy and unstable.

Problem Solving: Determining Aromaticity

Now that I've shown you why aromatic rings are so stable, and why anti-aromatic rings are so unstable, I show how you can determine whether a ring system is aromatic, anti-aromatic, or non-aromatic.

For a molecule to be aromatic, it must meet the following four conditions:

- It must be a ring.
- It must be flat (planar).
- It must have in each atom of the ring a *p* orbital that's orthogonal to the plane of the ring. In other words, no atom in the ring can be sp^3 hybridized.
- It must have a Hückel number of pi electrons, following the $4n + 2$ rule.

If the molecule meets the first three conditions, but only has $4n\pi$ electrons, the molecule is *anti-aromatic.* If the molecule fails any or all of the first three conditions, then the molecule is *non-aromatic.* I now give some details about each of these points.

The first condition is that only rings can be aromatic. Acyclic systems cannot be aromatic.

The second condition involves the shape of the ring. Ringed systems can be flat or three-dimensional. Most conjugated ring systems are flat in order to maximize the overlap between the *p* orbitals. But some exceptions exist. Cyclodecapentaene, for example, shown in Figure 13-11, is puckered because two hydrogens in the ring are pushed into each other's space, and the ring is forced out of planarity so that the hydrogens can occupy separate spaces. Because of its nonplanar structure, cyclodecapentaene is non-aromatic. Removing the two hydrogens and replacing them with a carbon bond to make naphthalene erases this problem; naphthalene is planar (and aromatic).

Cyclooctatetraene (Figure 13-12) is another example of a molecule that has alternating double bonds around the ring but isn't planar. Instead, this ring system adopts a puckered tub-shaped conformation. Why? Because if it

remained flat, it would become anti-aromatic as a result of having a non-Hückel number of pi electrons (8)! Because anti-aromatic systems are so unstable, this compound puckers and sacrifices the p orbital overlap so that it won't have to endure the pain of being anti-aromatic.

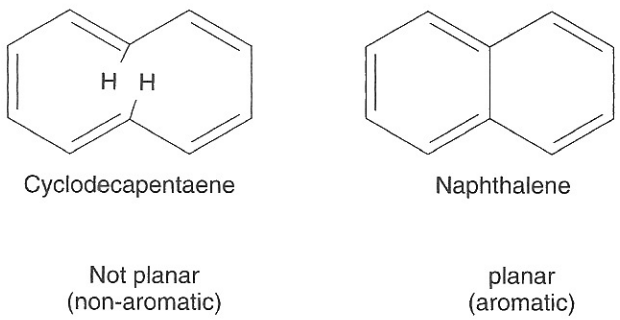


Figure 13-11: The nonplanar and planar rings of cyclodecapentaene and naphthalene.

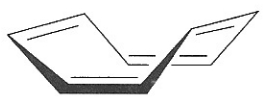


Figure 13-12: Cyclooctatetraene.

The third condition involves the orbitals. Aromatic systems must have an unbroken ring of *p* orbitals, so any ring that contains an sp^3 hybridized carbon will not be aromatic. Cycloheptatriene, shown in Figure 13-13, is non-aromatic because one of the ring carbons is sp^3 hybridized. However, carbocations (positively charged carbons) are sp^2 hybridized (and have an empty *p* orbital), so the cycloheptatriene cation has an unbroken ring of *p* orbitals and is an aromatic compound.

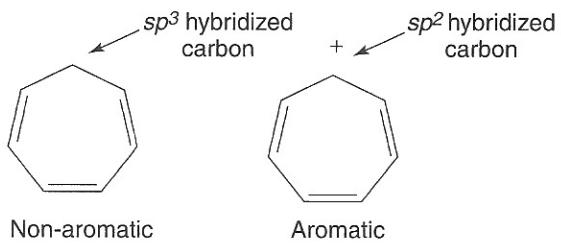


Figure 13-13: The non-aromatic cycloheptatriene molecule and the aromatic cycloheptatrienecation.

Finally, to be aromatic, a ring must have a Hückel number of electrons ($4n + 2$). Table 13-1 gives solutions to these equations for low values of n.

Table 13-1 Pi Electron Counts

Integer (n)	*Aromatic Numbers (4n + 2)*	*Anti-aromatic Numbers (4n)*
0	2	—
1	6	4
2	10	8
3	14	12
4	18	16

One tricky aspect of counting the number of electrons in the pi system is when the ring contains heteroatoms (like O, S, N). How do you know which lone pairs to count as part of the pi system and which to ignore (see Figure 13-14)?

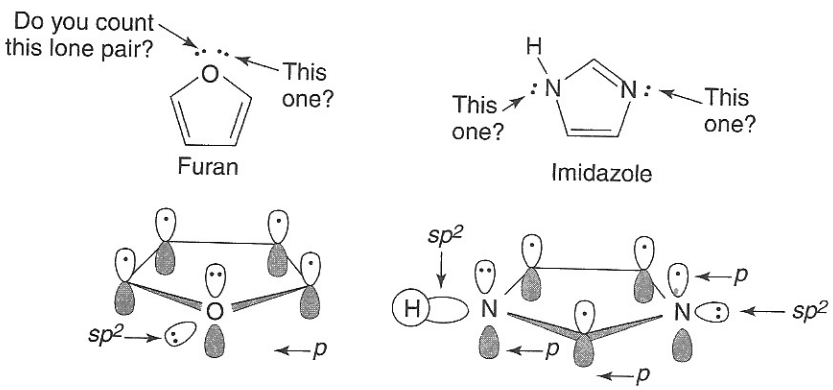


Figure 13-14: Counting pi electrons on hetero-atoms.

The long answer is that you have to draw out the orbitals to see which lone pair electrons would go into the pi system and which ones wouldn't. For furan, one lone pair from the oxygen would go into the p orbital (pi system), and one would go into an sp^2 hybridized orbital orthogonal to the ring. So the oxygen in furan would contribute two electrons to the pi system.

But wait a minute! Mustn't the oxygen in furan be sp^3 hybridized because the oxygen has four substituents (and lone pairs count as a substituent, see Chapter 2)? Not necessarily. While the general rule of counting substituents to determine hybridization holds true in most cases, it fails when an atom with a lone pair is adjacent to a double bond (that is, when it's conjugated).

In those cases, the atom with the lone pair will *rehybridize* from sp^3 to sp^2 so that it can conjugate the lone pair of electrons with the double bond.

Both furan and imidazole have six pi electrons and are aromatic. (Can you look at the orbital diagrams in Figure 13-14 and see that that's the case?)



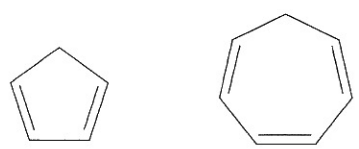
Here's a time-saving tip so you don't have to draw out the orbitals of heteroatom-containing rings every time. Heteroatoms (O, S, N) double bonded to other atoms in a ring cannot contribute their lone pairs to the pi system, because their *p* orbital is already being used to make the double bond. (Refer to Figure 13-14, and notice the orbitals of the double-bonded nitrogen in imidazole.) Heteroatoms only singly bonded to other atoms in a ring can contribute one lone pair to the pi system, but not two because only one lone pair can be in the pi system; the other lone pair will be in an sp^2 hybridized orbital orthogonal to the pi system. (Refer to Figure 13-14, and notice the orbitals of the singly bonded oxygen in furan.)

Problem Solving: Predicting Acidities and Basicities

Two of the most common problem types, when dealing with aromatic compounds, are predicting the acidities and the basicities of double-bond containing rings, including aromatic rings. These problems are designed to see if you can apply aromaticity on your own and understand that aromaticity is a stabilizing feature of molecules.

Comparing acidities

One common question is to ask which one of two double-bond containing rings is more acidic, such as the molecules in Figure 13-15. As with any acid-base reaction in which you need to compare acidity, you should look to see which acid has the more stable conjugate base.



Cyclopentadiene Cycloheptatriene

Figure 13-15: Cyclopentadiene and cycloheptatriene.



Stronger acids have more stable conjugate bases

Looking at the conjugate bases of both molecules (Figure 13-16), you see that both compounds have rings that are entirely conjugated, but one has six pi electrons (cyclopentadienyl anion), while the other has eight pi electrons (cycloheptatrienyl anion). Thus, the conjugate base with six pi electrons is aromatic, and should be more stable than the ring with eight pi electrons, which cannot be aromatic. Based on this analysis, cyclopentadiene must be more acidic than cycloheptatriene. A general feature of these problems is that the conjugate base of one of the molecules will be aromatic, while the other one won't be. The more acidic compound is the one that becomes aromatic (and, therefore, more stable) upon deprotonation.

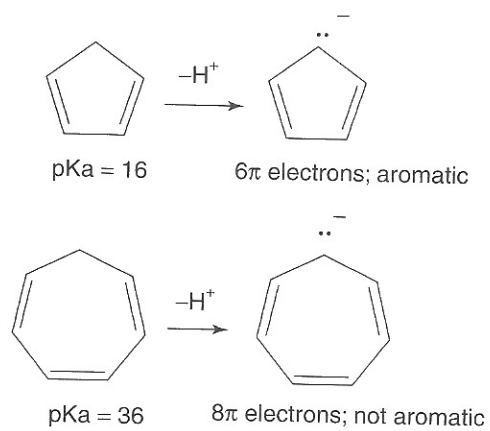


Figure 13-16: Comparing acidities of rings.

Comparing basicities

Another common question type is to compare or predict the basicity of nitrogen atoms in aromatic compounds. For example, can you predict which nitrogen is more basic in the aromatic molecule imidazole, shown in Figure 13-17?

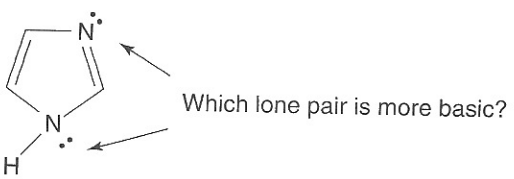


Figure 13-17: Comparing the basicities of the nitrogens in imidazole.

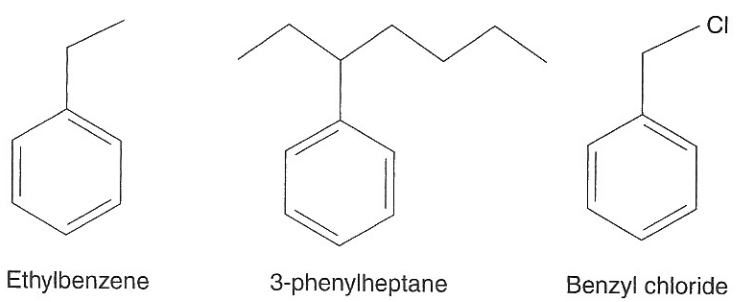
To determine the strength of a base, you look at the stability of the conjugate acid. Protonating the bottom nitrogen in the imidazole in Figure 13-17 disrupts the aromaticity of the ring, because that nitrogen lone pair is part of the pi system. (Upon protonation, the lone pair is tied up in a bond to hydrogen and can no longer contribute to the aromaticity.) Protonating the top nitrogen doesn't disrupt the pi system (or the aromaticity) of imidazole because the lone pair is situated in an sp^2 hybridized orbital, and is not part of the pi system. (Refer to Figure 13-14 for the orbital drawings of imidazole.) Therefore, the top nitrogen is much more basic than the bottom nitrogen, because the top nitrogen is much happier with an added hydrogen than the bottom nitrogen is. The general feature of these problems is that nitrogens whose lone pairs are not involved in the pi system are more basic than nitrogens with lone pairs in the pi system.

Naming Benzenes and Aromatics

Substituted benzenes are named with the parent name of — *surprise!* — benzene. Thus, benzene with an ethyl group is named ethylbenzene, as shown in Figure 13-18. When you have an alkyl chain that has more carbons than the aromatic ring, the alkyl portion becomes the parent group. When benzene is named as a substituent, it's called a *phenyl group* (often abbreviated Ph), as in 3-phenylheptane. A general term for an aromatic ring as a substituent is the word *aryl.* A benzene with a methylene (CH_2) portion is known as a *benzyl group,* as shown in Figure 13-19.



Don't confuse a phenyl ring with a benzyl group.



Ethylbenzene 3-phenylheptane Benzyl chloride

Figure 13-18: The names of some substituted benzenes.

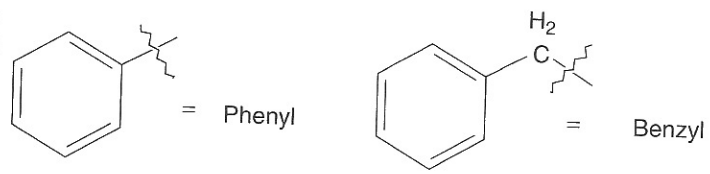


Figure 13-19: The phenyl ring and the benzyl group.

Common names of substituted benzenes

One thing that you might find frustrating about aromatic compounds is that substituted benzenes are known by many common names. Methylbenzene, for example, is almost always called toluene. These names simply must be memorized. Some of the most common substituted benzenes are shown in Figure 13-20.

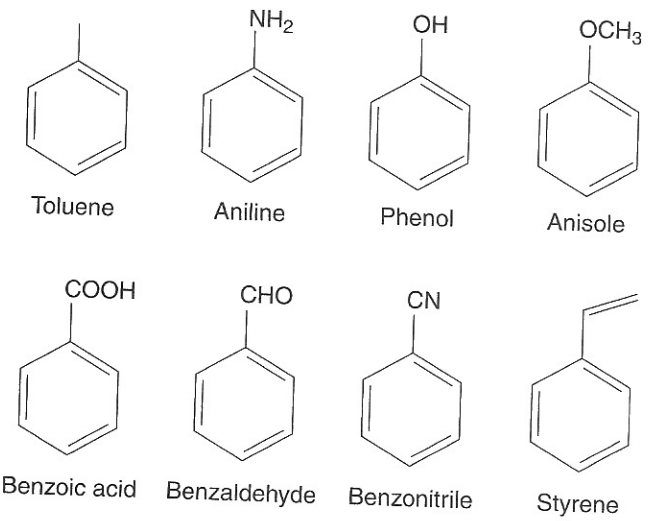


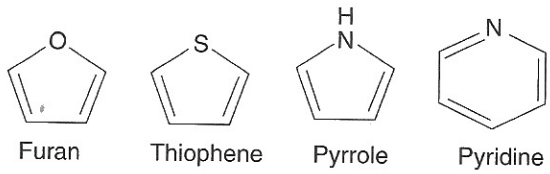
Figure 13-20: The common names of some substituted benzenes.



Many professors like to test whether you can remember the common names of compounds by giving synthesis problems on exams using the common names of the starting materials. For example, you might get a problem that says, "Starting with toluene, propose a synthesis to make compound X." If you don't know the structure of toluene, you're up a creek on that problem without a you-know-what, even if you could have done the synthesis had you known the structure.

Names of common aromatics

The names of aromatics other than benzene are shown in Figure 13-21. For practice, you might want to see if you can determine how many pi electrons each of these rings contains. (They all have six pi electrons, but from where do these electrons come?)



Furan Thiophene Pyrrole Pyridine

Figure 13-21: The names of some common aromatics.

Bringing Out the Howitzers: Electrophilic Aromatic Substitution of Benzene

Unlike the double bonds of alkenes, the double bonds in benzene are only weakly *nucleophilic* (nucleus loving), so you need powerful *electrophiles* (electron lovers) to make benzene react. You usually have to throw a full positive charge on the electrophile to make it strong enough to react with benzene. For example, Br_2 reacts with alkenes, but does not react with benzene. However, positively charged bromine, Br^+, does react with benzene, because positively charged species are much more electrophilic than neutral species are. Unlike the reaction of bromine with alkenes (in which you get an addition reaction across the double bond), when benzene is reacted with the bromine ion (Br^+), you get substitution reactions (in which the electrophile substitutes for hydrogen).

Reacting benzene with electrophiles is a reaction called *electrophilic aromatic substitution,* and the general mechanism for this reaction is shown in Figure 13-22. In the first step of the mechanism, one of the double bonds in benzene attacks the positively charged electrophile (E^+) to make a cation. This intermediate cation is stabilized by resonance (can you draw out the other two resonance structures?), but it's non-aromatic (because the ring has an sp^3-hybridized carbon). In the second step, when a base (abbreviated $B:^-$) plucks off a proton adjacent to the carbocation, the aromatic ring is re-formed to make the substituted benzene.

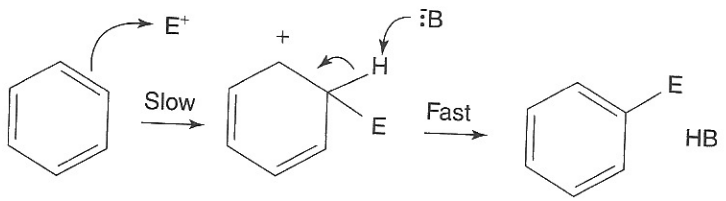


Figure 13-22: The mechanism of electrophilic aromatic substitution.

Figure 13-23 shows the reagents that you use to make different types of positively charged electrophiles. These reagents can be used to nitrate, brominate, chlorinate, or sulfonate benzene rings. These electrophiles all add to benzene in the fashion shown in Figure 13-22. The alkylation and acylation reactions are discussed in more detail below.

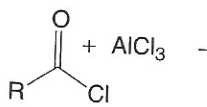
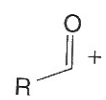
	Reagents	Electrophile (E^+)	Biproducts
Nitration	$HNO_3 + H_2SO_4$	$O{=}\overset{+}{N}{=}O$	H_2O / HSO_4^-
Bromination	$Br_2 + FeBr_3$	Br^+	$FeBr_4^-$
Chlorination	$Cl_2 + FeCl_3$	Cl^+	$FeCl_4^-$
Sulfonation	$SO_3 + H_2SO_4$	$O{=}\overset{+}{S}{=}O$ (with O—H)	HSO_4^-
Alkylation	$R{-}Cl + AlCl_3$	R^+	$AlCl_4^-$
Acylation			$AlCl_4^-$

Figure 13-23: Generating electrophiles for electrophilic aromatic substitution reactions.

Adding alkyl substituents: Friedel-Crafts alkylation

One way to alkylate benzene rings was proposed by Charles Friedel and James Crafts. Reacting alkyl chlorides with the Lewis acid aluminum trichloride makes carbocations, they discovered, as shown in Figure 13-24. Carbocations are electrophilic enough to react with benzene to form alkyl benzenes by the same mechanism outlined in Figure 13-22.

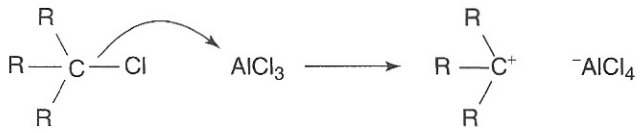


Figure 13-24: Making carbocations.

Carbocations, though, are like naughty little children. As illustrated in Chapter 8 with the addition of HCl to alkenes, carbocations can — and will — rearrange if doing so makes a more stable carbocation.



Tertiary cations are more stable than secondary cations, which are more stable than primary cations.

For example, reacting benzene with propyl chloride and aluminum trichloride makes isopropyl benzene as the major product, with the expected product, propyl benzene, as the minor product. See Figure 13-25 for the products of this reaction.

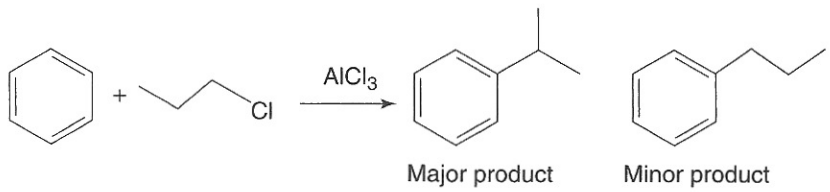


Figure 13-25: The Friedel-Crafts alkylation.

The reason for this reaction not giving the expected product is that the primary cation can rearrange to the more stable secondary carbocation by a hydride shift, as shown in Figure 13-26. The addition of this secondary cation to benzene yields isopropyl benzene as the major product. Because of these rearrangements, adding straight-chain alkyl groups to benzene is difficult using the Friedel-Crafts alkylation reaction.

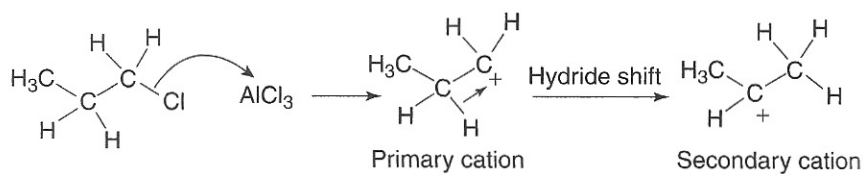


Figure 13-26: The carbocation rearrangement in the Friedel-Crafts reaction.

Overcoming adversity: Friedel-Crafts acylation

To stop these pesky rearrangements that lead to undesired products, Friedel and Crafts came up with an acylation reaction (pronounced ay-sill-AY-shun). Taking an acid chloride (RCOCl) and adding aluminum trichloride makes an acylium cation, as shown in Figure 13-27. Acylium ions are stabilized by resonance and don't rearrange.

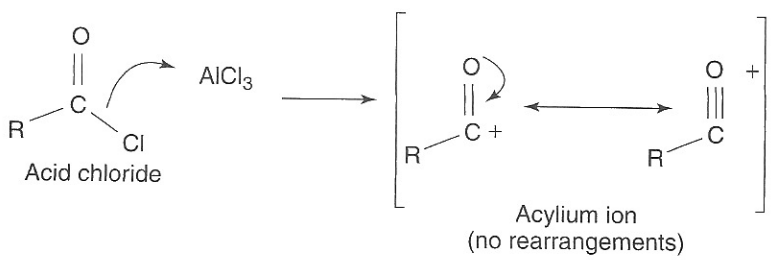


Figure 13-27: Making acylium cations.

These acylium ions then add to benzene to make aryl ketones, as shown in Figure 13-28. Aryl ketones can be conveniently reduced with hydrogen and palladium on carbon (Pd/C) to alkyl aromatics. (Regular ketones not next to benzene rings, however, are untouched by these reagents.) Although it requires an additional step, this reaction sequence — acylation followed by reduction — is a handy way of making alkyl benzenes without worrying about carbocation rearrangements giving you undesired products.

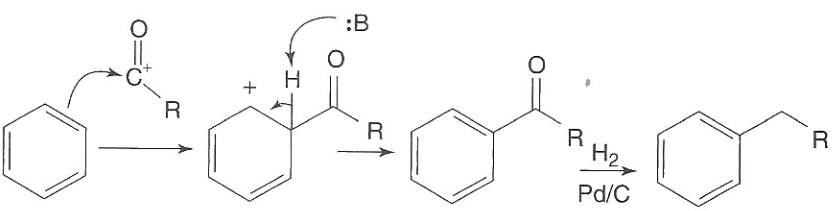


Figure 13-28: The Friedel-Crafts acylation followed by reduction.

Reducing nitro groups

A convenient way of making aryl amines is by reducing nitro groups. These groups can easily be reduced by the addition of tin chloride ($SnCl_2$) in a little acid, as shown in Figure 13-29.

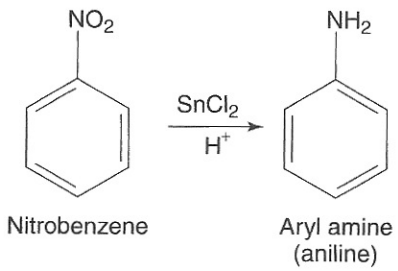


Figure 13-29: Nitro reduction and the formation of an aryl amine.

Oxidation of alkylated benzenes

Potassium permanganate is a powerful oxidizing reagent. In the presence of acid, this reagent takes alkyl benzenes, chews them up, and spits out aryl carboxylic acids (benzoic acids, refer to Figure 13-21), as shown in Figure 13-30. Any alkyl side chain that has a hydrogen adjacent to the phenyl ring will be oxidized to a carboxylic acid (a COOH group). If the alkyl side chain has no hydrogen adjacent to the ring, it will be left untouched.

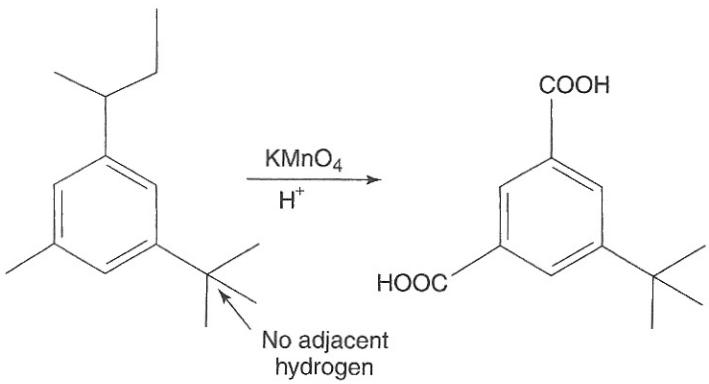


Figure 13-30: Permanganate oxidation.

Adding Two: Synthesis of Disubstituted Benzenes

Now you know the reagents that add different groups to benzene. But what if you want to synthesize disubstituted benzenes? After adding the first group, three locations are possible for the next group to add to, as shown in Figure 13-31. One possibility is for the next group to add *ortho* — organic-speak for

adding to the carbon adjacent to the substituent. The group could also add *meta* (two carbons away from the first group) or it could add *para* (on the opposite side of the ring from the original group).

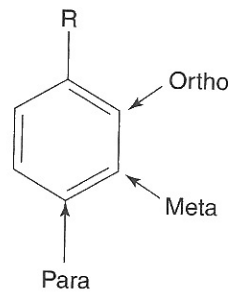


Figure 13-31: The ortho, meta, and para positions.

Where the second substituent adds — either ortho, meta, or para to the first substituent — depends on the nature of the group already attached to the benzene ring. Think of the substituents already on the ring as traffic controllers at an airport, directing the electrophile to land at certain runways (either ortho, meta, or para, in this case). Electron-donating substituents activate the ring (that is, they make the ring react faster than an unsubstituted benzene reacts), and they tell the incoming electrophile to land either at the ortho or the para position. With electron-donating substituents, you usually get a mixture of the ortho and para products. Electron-withdrawing groups on the ring, on the other hand, deactivate the benzene ring toward electrophilic attack (making the reaction slower than is the case with an unsubstituted benzene) and these electron-withdrawing groups tell the incoming electrophile to land at the meta position.

Why do you get different substitution products depending on whether the ring is substituted with electron donors or electron acceptors? The answer is that electrophiles add to the benzene ring on the atom that generates the most stable intermediate cation. With electron donors on the ring, the intermediate carbocation resulting from ortho or para addition is more stable than the cation deriving from meta addition. With an electron-withdrawing substituent on the ring, the intermediate carbocation from meta addition is more stable than the carbocation resulting from ortho or para addition.

In the following sections, I show you why the cation resulting from ortho-para addition with electron donors is more stable than the meta-derived cation. I also discuss why the cation resulting from meta addition with electron acceptors is more stable than the cations resulting from ortho or para addition.

Electron donors: Ortho-Para activators

If you brominate anisole, for example, as shown in Figure 13-32, you get addition of the bromine to the ortho and para positions, but not to the meta position. This is because methoxy groups (OCH_3) are pi electron donors, and so direct all incoming electrophile traffic into the ortho and para positions.

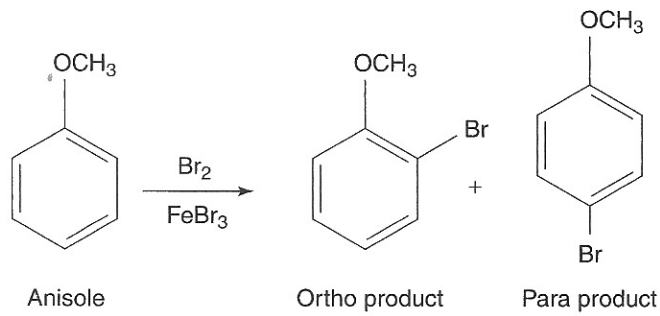


Figure 13-32: Bromine addition to anisole.

You can see why the methoxy group directs to the ortho and para positions by looking at the intermediate carbocation for both the para addition and the meta addition. With para addition (and with ortho addition), a much more stable intermediate carbocation is formed compared to the cation that's formed when the substituent adds in the meta position. The intermediate carbocation that results from para addition has four resonance structures, shown in Figure 13-33, with one of these resonance structures being particularly good because all valence octets on all atoms are filled. (This good resonance structure is boxed in the figure.) The carbocation resulting from meta addition, on the other hand, has only three resonance structures, none of which have all atoms with filled valence octets. Recall the general rule that stability increases as the number of resonance structures increases. Thus, with electron donors on the aromatic ring, ortho-para products are selectively formed.

Electron-withdrawing groups: Meta directors

Of course, the situation is reversed when the aromatic ring is substituted with electron-withdrawing substituents rather than electron-donating substituents. Electron-withdrawing substituents direct all incoming electrophiles to the meta position. Take the bromination reaction of nitrobenzene, for example, shown in Figure 13-34. Nitro groups are electron-withdrawing groups, and so bromine adds to the meta position.

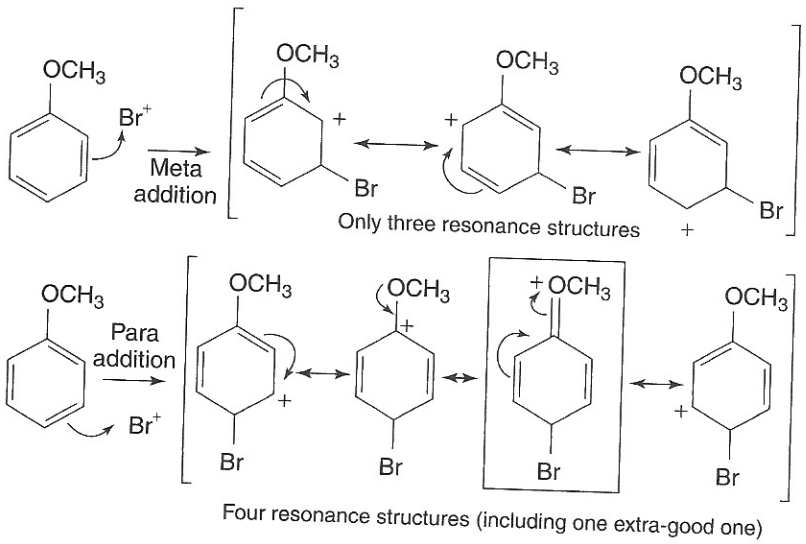


Figure 13-33: The relative stabilities of intermediate carbocations resulting from meta and para addition to anisole.

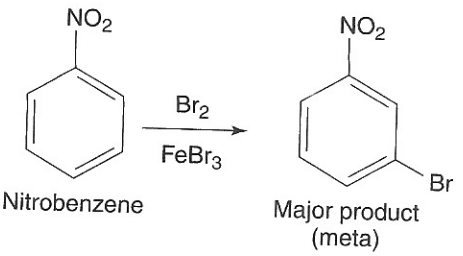


Figure 13-34: The bromine addition to nitrobenzene.

To see why the meta product is formed instead of the ortho-para products, compare the intermediate cation formed as a result of para bromine addition to the cation generated from meta addition (see Figure 13-35). The intermediate carbocation resulting from para addition (or ortho addition) has three resonance structures, but one of them is a particularly bad resonance structure because the structure has two adjacent positive charges (and like charges repel). Thus, this bad resonance structure doesn't contribute much to the overall resonance hybrid. The cation resulting from meta addition also has three resonance structures, but none of them are bad. Thus, for benzenes substituted with electron-withdrawing groups, the cation resulting from meta addition is more stable than the cation resulting from either ortho or para addition.



The main point to remember here is that electron-donating groups direct substitution to the ortho and para position, while pi electron-withdrawing groups direct substitution to the meta position.

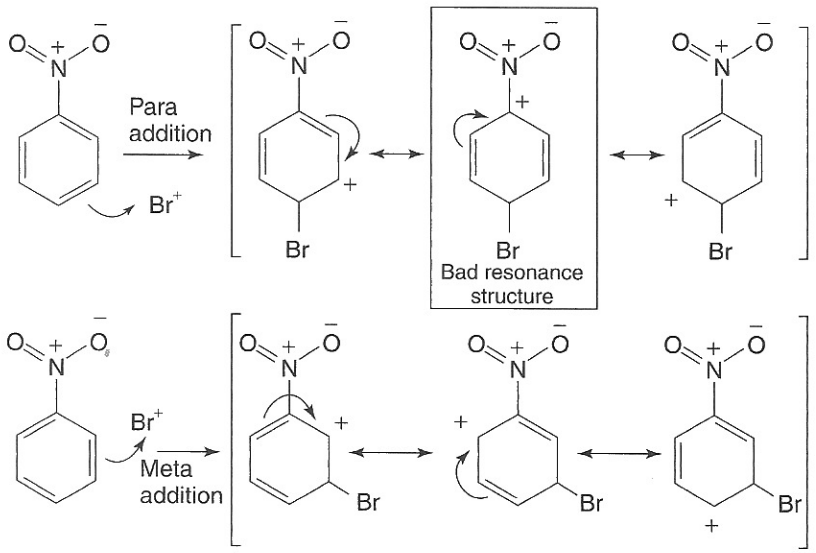


Figure 13-35: The relative stabilities of intermediate carbocations resulting from para and meta addition to nitrobenzene.

So far, I've talked about electron-donating and electron-withdrawing substituents, without really saying what I mean. Any substituent whose first atom (the one that's attached to the benzene ring) has a lone pair will be a pi electron donor to the phenyl ring, as shown in the resonance structure in Figure 13-36. Note that the resonance structures show that substituents that are pi donors add electron density to the ortho and para positions of the ring. Thus, pi donors activate the benzene ring toward *electrophilic attack* (attack by incoming electrophiles) at the ortho and para positions. Adding electron density to the benzene ring makes the ring more *nucleophilic* (that is, more nucleus loving) and activates the ring. Therefore, pi donors are considered ring activators.

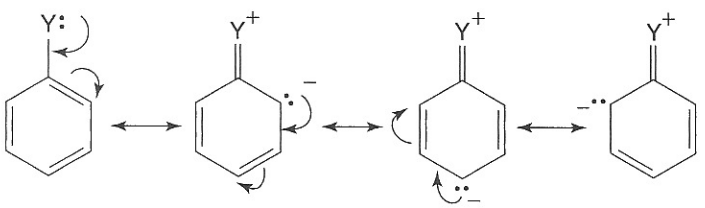


Figure 13-36: Pi electron donors to the phenyl ring.

The only exceptions are the halogens, which are not terribly good pi donors. They deactivate the ring as a result of being highly electronegative groups, pulling electrons away from the benzene ring toward themselves, making the ring less nucleophilic. But even though halogens are ring deactivators, they're still ortho-para directors.

Pi-withdrawing groups (such as NO_2 groups, carbonyl groups, CN, and so on) pull electrons away from the ring and deactivate it, making the ring less nucleophilic. Pi electron-withdrawers are thus ring deactivators. A deactivator means that the reaction of benzenes substituted with these substituents will be slower than the reaction of unsubstituted benzene. Pi electron-withdrawing substituents are meta directors. Table 13-2 outlines the nature of different substituents.

Table 13-2 The Nature of Aromatic Substituents

Ortho-Para Directing			*Meta Directing*
Strongly Activating	Weakly Activating	Deactivating	Deactivating
OH	Alkyl	Halogens (F, Cl, Br, I)	NO_2
OCH_3	Phenyl		—COR (COOH, COOR, CHO, and so on)
NH_2			CN
NR_2			SO_3H



Here's a tip for remembering Table 13-2: Any substituent whose first atom (the one attached to the benzene) contains a lone pair of electrons will be an ortho-para director (although not necessarily a ring activator). Those substituents without a lone pair on the first atom will likely be meta directors (with the exception of alkyl groups and aromatic rings, which are ortho-para directors).



For performing multistep synthesis, the reduction of a nitro group to make an aryl amine is a way of converting a meta director into an ortho-para activator. The oxidation of an alkylated benzene (to make an aryl carboxylic acid) is a way of converting an ortho-para activator into a meta director.

Problem Solving: Synthesis of Substituted Benzenes

When thinking about the synthesis of *polysubstituted benzenes* (benzenes substituted more than once), remember that the order of substituent addition is crucial. You have to put the substituents on in the right order so that they will direct the next substituent to the right place.

For example, how would you synthesize 3-bromo-1-ethylbenzene shown in Figure 13-37? First, you should notice that the substituents are meta to each other. That means that the first substituent that you add should be a meta director in order to get the next substituent in the meta position. But the substituents — the ethyl group and the bromine — are both ortho-para directors! How are you going to get them meta to each other? At some point, one of them must have been a meta director that then got converted into the ortho-para substituent.

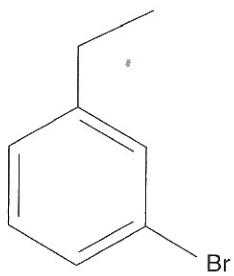


Figure 13-37: 3-bromo-1-ethylbenzene.

In the case of 3-bromo-1-ethylbenzene, the ethyl group could be added by a Friedel-Crafts acylation, as shown in Figure 13-38. Acyl groups are meta directors. The bromine could then be added and would go meta to the acyl group. The acyl group could then be reduced into the alkyl portion, as shown in the last step of Figure 13-38. The key to this synthesis is the order — switching any of the steps would lead to the wrong product.

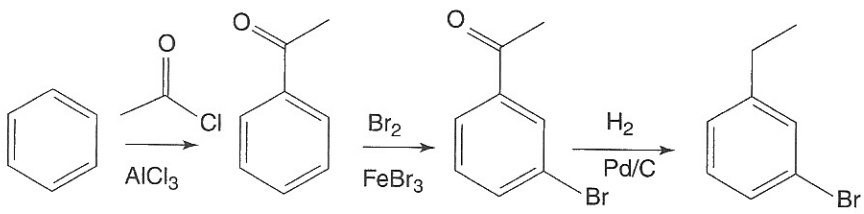


Figure 13-38: The synthesis of a disubstituted benzene.

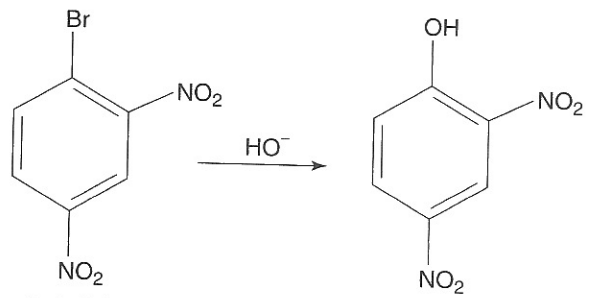


The key to mastering aromatic synthesis problems is to add substituents in the correct order.

Nucleophiles Attack! Nucleophilic Aromatic Substitution

I've shown you how benzene can act as a nucleophile (nucleus lover), reacting with powerful electrophiles in the electrophilic aromatic substitution reaction. Benzene can also act as an electrophile when the ring is sufficiently activated toward nucleophilic attack. When benzene is activated toward nucleophilic attack, strong nucleophiles can displace leaving groups substituted on the ring (usually a halide).

Benzene rings activated toward nucleophilic attack include those that are substituted with strong electron-withdrawing groups in the ortho and para positions (groups like NO_2, CN, COR, and so on). Substituted benzenes that are not activated with powerful electron-withdrawing groups will not undergo nucleophilic aromatic substitution. For example, 1-bromo-2,4-dinitrobenzene, shown in Figure 13-39, is activated toward nucleophilic attack because it has two powerful electron-withdrawing groups (NO_2) ortho and para to the leaving group (Br). The addition of hydroxide ion (HO^-) displaces the bromide.



1-bromo-2,4-dinitrobenzene

Figure 13-39: Nucleophilic aromatic substitution.

The mechanism of the addition is shown in Figure 13-40. First, the nucleophile (HO^-) attacks the benzene ring at the carbon, holding the leaving group, generating a *carbanion* (a negatively charged carbon). This carbanion is stabilized by the electron-withdrawing groups (NO_2) on the ring (and by additional resonance structures that are not shown). The anion can then displace the bromine leaving group to regenerate the substituted aromatic ring.



Nucleophilic aromatic substitution only occurs with benzene rings activated by strong electron-withdrawing groups.

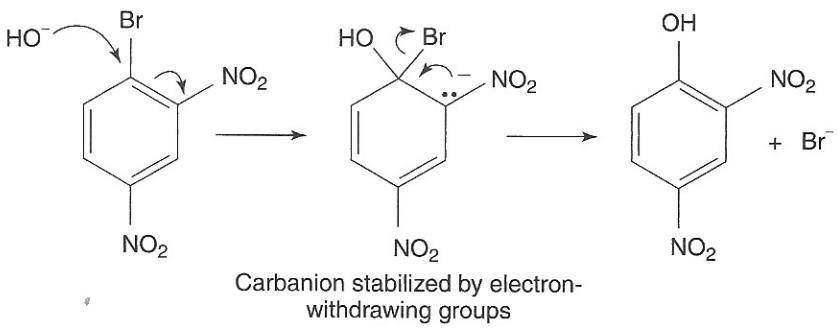


Figure 13-40: The mechanism of nucleophilic aromatic substitution.

A somewhat less useful but still highly interesting reaction of benzene is the reaction of a halobenzene (like bromobenzene or chlorobenzene) with a strong base (like hydroxide) at high temperature and pressure. Because the aromatic ring is not activated for nucleophilic attack by electron-withdrawing substituents, you can't get nucleophilic aromatic substitution. Instead, you get elimination, as shown in Figure 13-41, to make a weird intermediate called a benzyne. *Benzyne* is a highly unstable intermediate, consisting of a benzene ring with a triple bond. Nucleophiles (abbreviated ⁻:Nuc in Figure 13-41) quickly add to benzyne to make substituted benzenes.

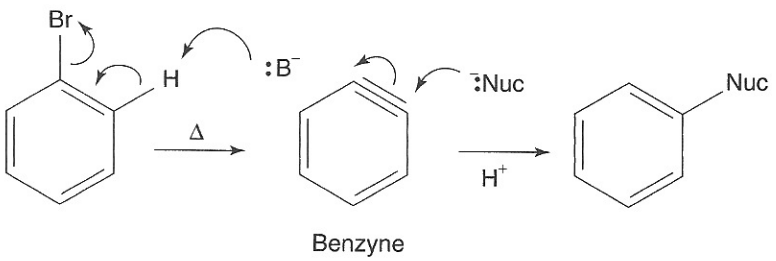


Figure 13-41: Benzyne reactions.

An example of benzyne addition is shown in Figure 13-42. In this case, the base that's used to make the benzyne and the nucleophile that reacts with the benzyne is hydroxide (⁻OH). Note that because the nucleophile can add to either side of the benzyne, you get a mixture of products. Because you often get product mixtures with substituted benzenes, and because this reaction requires high temperature and pressure, this reaction is not quite as generally useful as electrophilic or nucleophilic aromatic substitution.

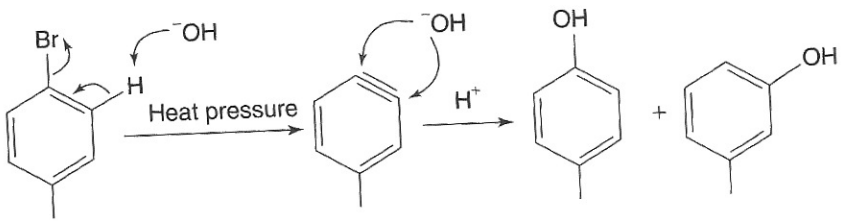


Figure 13-42: An example of benzyne addition.

Part IV

Spectroscopy and Structure Determination

The 5th Wave By Rich Tennant



"You can take that old jar for your science project, I'm sure I have some baking soda you can borrow, and let's see, where's that old particle accelerator of mine... here it is, in the pantry."

In this part . . .

Pretend you're an organic chemist. A biochemist you collaborate with has just isolated a deadly neurotoxin from a marine shellfish that has killed several people who have ingested it. He gives you a vial with a small sample of the pure, white powder, and asks you to determine its chemical structure. With lives at stake, how do you do it? with spectroscopy.

By using IR and NMR spectroscopy, in addition to mass spectrometry, structures of unknown compounds can be determined. By using all three of these techniques in conjunction with each other, many structures can be determined without any other information. In this part, I cover the tools that organic chemists use for structure identification, and I show you how to make sense of the data to figure out the structures of unknown compounds.

Chapter 14

A Smashing Time: Mass Spectrometry

In This Chapter

- Seeing how mass spectrometry works
- Breaking down a mass spectrum
- Predicting fragments formed in the mass spectrometer
- Examining isotope effects
- Working problems with mass spec

Imagine trying to determine how a watch is put together by whacking it with a mallet and examining all of the little pieces. KAPLOW! A spring here, a cog there. This process may not be the most elegant examination — and it probably won't please your friend whose watch you "borrowed" — but it will give you some information about the different parts that made up that watch. Such an examination probably wouldn't give you enough information to determine exactly how the watch fit together, but you would certainly be more informed about what was inside the watch after your experiment than you were before.

Furthermore, certain brands of watches would likely break apart in different ways. If you smashed a particular brand of watch, say Watch Brand A, you may find that in most cases you break off the clasp when you hit it with a mallet; with Watch Brand B, you may find that you break off the casing more of the time but leave the clasp intact.

That's sort of how mass spectrometry works — with a molecule, of course, instead of a watch. A mass spectrometer works by smashing a molecule into bits. Instead of viewing all of the shattered pieces, though, a mass spectrometer weighs them. The weights of these fragments give clues about the structure of the molecule itself. And, like different kinds of watches, different kinds of molecules break apart in distinct ways in a mass spectrometer.

In this chapter, I talk about how mass spectrometry works, how to interpret a mass spectrum, and how to figure out what fragments will most likely be formed from a given structure.

Defining Mass Spectrometry

Mass spectrometry is really quite different than spectroscopy. You often hear or read the words "mass spectroscopy." But by definition, spectroscopy involves light, and mass spectrometry doesn't involve light at all. Still, like spectroscopy (see Chapters 15 and 16), mass spectrometry (or "mass spec") provides valuable information about the structure of a compound. In fact, modern organic chemists use mass spectrometry nearly as much as NMR (see Chapter 16) in order to determine the structures of compounds. Perhaps this is because, in addition to giving clues about the structures of unknown molecules, mass spectrometry appeals to chemists' childlike urges to smash things — albeit on very tiny scales.

Taking Apart a Mass Spectrometer

Here's a very general rundown of how a mass spectrometer works, free for the moment of technical names and jargon (see Figure 14-1). The sample containing the unknown compound is first injected into the spectrometer through an inlet, and is then vaporized by heating it under a vacuum. The vaporized sample is then pushed by an inert gas into the "smasher" where the sample is clobbered and broken into little bits. Some particles come out of the "smasher" with an electrical charge and some come out uncharged. All of the charged bits (called ions) move along into the sorter, which separates the bits according to how much they weigh. All of the uncharged bits are discarded. The remaining charged particles then hit a detector, which determines how many bits of each weight there are, and plots the data on the mass spectrum. This spectrum shows the molecular weight of each fragment versus the number of fragments with that weight that hit the detector.

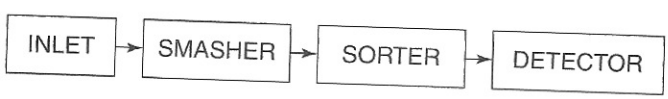


Figure 14-1: The basic parts of a mass spectrometer.

Now I talk about the specifics of each of these parts.

The inlet

Mass spectrometry is performed in the gas phase. Therefore, the first thing that happens after the sample is injected into the spectrometer is that the sample is vaporized by heating the sample under low pressure. After the sample is in the gas phase, it's pushed into the smasher by the flow of an inert gas (usually helium).

Electron ionization: The smasher

A mass spectrometer can use many different "mallets" to *ionize* molecules. *Ionize* is organic-speak for smashing the neutral molecules into charged fragments. The most common mallet is one that incorporates high-energy electrons (there are other kinds, but this is the most popular). Mass spectrometry using this type of smasher is termed *electron-ionization* mass spectrometry (EIMS). (On an exam, be sure to use this term, not "smasher.") In an electron-ionization mass spectrometer, the molecules are pushed through a stream of very high-energy electrons to ionize them. When one of these high-energy electrons crashes into the molecule, an electron is ejected from the molecule, as shown in Figure 14-2.

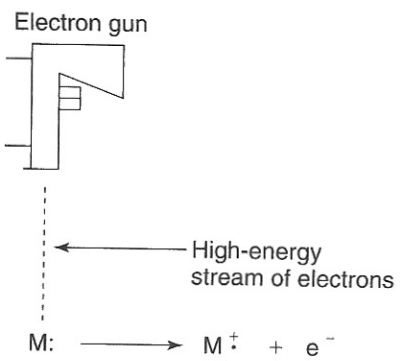


Figure 14-2: The ionization of molecules in the smasher of an electron-ionization mass spectrometer.

Both the smashing electron from the electron source (diagramed in the figure as an electron gun) and the electron that's kicked out of the molecule don't play any further roles in the process and are simply discarded. But each molecule that has had an electron knocked out becomes a species called a

radical cation (abbreviated $\dot{+}$). The "cation" portion of the name results from the fact that the molecule has lost an electron and is now positively charged, and the "radical" portion of the name comes about because one of its electrons is unpaired. For more on radicals, see Chapter 7. These radical cations can either remain in one big piece or spontaneously fragment further into several smaller pieces. (I talk more about this later.) In either case, all of the fragments move on toward the sorter and weigher.

The sorter and weigher

What happens after the molecules are smashed and become radical cations? Some of them stay as they are and move through the spectrometer to the weigher. Those pieces that stay whole give a peak in the mass spectrum called the *molecular ion peak,* or M+ peak. This molecular ion peak tells you the molecular weight of the molecule, because losing an electron doesn't really change the weight of the molecule (it's like a tractor trailer losing a lug nut). The molecular ion peak is the most important piece that's weighed by the mass spectrometer, because knowing the molecular weight of the unknown molecule is a very valuable piece of information when you're trying to determine its structure.

While some of the radical cations stay intact and lead to the molecular ion peak, others break down spontaneously into smaller bits. Most commonly, the radical cations break into two pieces, one piece that's a neutral radical, and one piece that's a positively charged cation (see Figure 14-3). For reasons I talk about later, only the charged cationic species is "seen" and weighed by the mass spectrometer. The neutral radicals are discarded and go undetected.

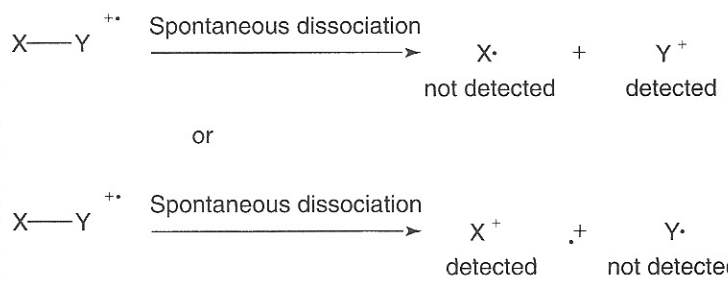


Figure 14-3: The dissociation of radical cations.

After the pieces have become charged by the smasher, they're sent through the weigher. This weigher, though, isn't like the scale that collects dust in your bathroom. Instead, because the fragments are charged, they can be weighed by accelerating them through the poles of a magnet. When charged

particles move through a magnetic field, they're *deflected* (pulled off course) by the magnetic field; all uncharged fragments are not deflected by the magnet and simply crash and burn into the walls of the spectrometer, never to be seen again. Therefore, only charged particles can hit the detector.

The weight of a fragment determines how much it will be deflected by the magnet. Light fragments are deflected a lot by the magnet, while heavier fragments are deflected less. With a low magnetic field strength, small particles will be bent the right amount by the spectrometer to hit the detector, while all the other fragments will crash and burn into the walls of the spectrometer. With a larger magnetic field strength, larger particles will curve the right amount to hit the detector. By varying the magnetic field strength (which is proportional to the weight of the fragment), the weights of the fragments can be determined.

Detector and spectrum

How many particles bend the right amount at a particular magnetic field strength is measured by the detector. On a mass spectrum, the molecular weight of the fragment is shown on the x-axis versus the relative number of fragments that hit the detector on the y-axis (the intensity). The most intense peak on the mass spectrum is arbitrarily assigned an intensity value of 100. The full mass spectrometer is shown in Figure 14-4.

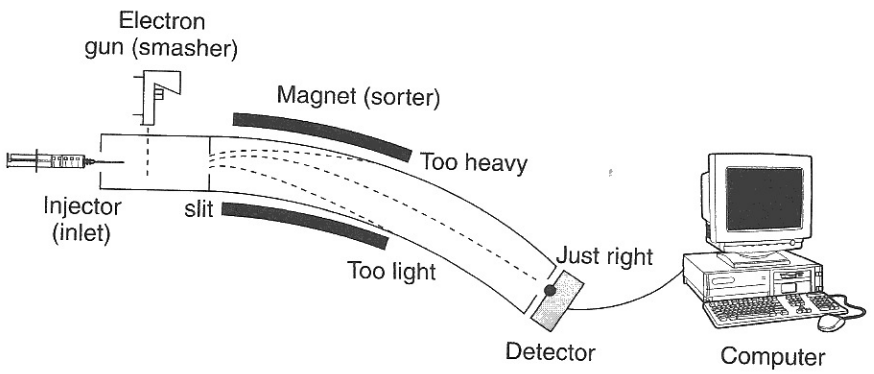


Figure 14-4: The inside of a mass spectrometer.



It's actually not the weight of the fragment that's measured on the x axis of the mass spectrum, but the mass (m) to charge (z) ratio (called the *m/z value*). A fragment that has a +2 charge will require a smaller magnetic field to deflect it toward the detector than a fragment that has a +1 charge, and will therefore show up on the mass spectrum at half the m/z value. However, since most

fragments simply have charges of +1 (and since the vast majority of undergraduate classes will not discuss fragments with more than one charge), the *m/z* axis is often simply said to represent the molecular weight of the fragment.

The Mass Spectrum

Figure 14-5 shows the mass spectrum for the molecule pentane (C_5H_{12}). This spectrum contains several peaks that are worth pointing out. The molecular ion peak, or M+ peak, is the peak at *m/z* 72, which represents the molecular weight of the molecule (72 g/mol). The tallest peak in the spectrum, which is always given a value on the y-axis of 100, is called the *base peak*. The base peak represents the most abundant fragment that hits the detector. In some spectra, the base peak is also the M+ peak, although in this case it's not.

The mass spectrum for pentane is fairly simple, but it still contains a lot of peaks, each of which represents a different fragment that was formed by electron ionization. Later in the chapter, I show you how to determine the structure of some of the most important fragments in the mass spectrum. Usually, though, you can't expect to be able to identify all of the peaks in a mass spectrum (or even most of them).

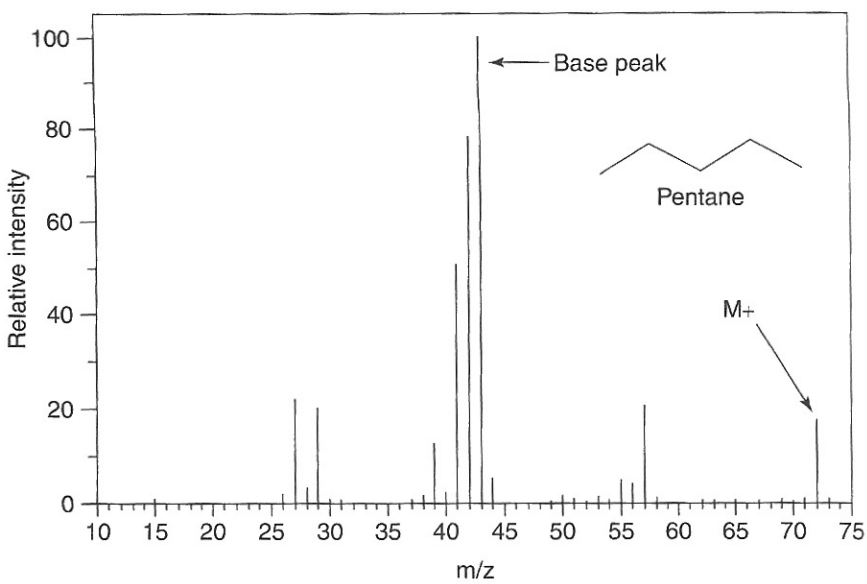


Figure 14-5: The mass spectrum for pentane (C_5H_{12}).

Kind and Caring: Sensitivity of Mass Spec

One of the most valuable features of mass spectrometry is its sensitivity. While NMR and IR spectroscopy usually require milligrams of material to do an analysis, mass spec requires only nanograms (10^{-9} grams) of material. This sensitivity is particularly useful for characterizing compounds isolated from biological systems in which many substances are produced and isolated in miniscule amounts. (The structure of the ketone chiloglottone, discussed in Chapter 5, was determined solely using mass spectrometry because it was isolated in such small amounts.) Unlike NMR and IR spectroscopy, however, the sample used to take a mass spec is nonrecoverable, so the tiny amounts that are required in order to obtain a spectrum are destroyed and cannot be recollected for later study.

Resolving the Problem: Resolution

In addition to its ability to detect tiny amounts of material, mass spectrometry can also weigh things with incredible accuracy. In other words, high-resolution mass spectrometers (HRMS) can determine the exact weight of a compound, enough to definitively identify a compound's molecular formula, which is a very valuable piece of information. For example, the compounds with molecular formulas C_3H_6 and C_2H_2O each have a molecular weight of about 42 g/mol. So how can a mass spectrometer distinguish between them? The answer lies in the fact that the mass spectrometer determines the weight of the molecular ion (M^+) fragment with accuracy of several digits after the decimal point. Both C_3H_6 and C_2H_2O have molecular weights that are approximately — but not exactly — 42 g/mol. The molecular mass system is set up so that ^{12}C has a mass of exactly 12.0000 g/mol, and the weights of all other atoms are calibrated against this number. Therefore, elements other than carbon don't have masses that are exact whole numbers. By this system, the exact mass of C_3H_6 is 42.0469 g/mol and the exact mass of C_2H_2O is 42.0105 g/mol.

In this example, the masses of these two compounds differ by about 0.036 g/mol; this is a very small difference, really, but a difference that's large enough to be distinguished by a good mass spectrometer. A mass spectrometer with a high enough resolution can detect these differences, and the correct molecular formula can therefore be deduced (usually, using a computer program). In this case, a mass spectrometer that's accurate to the second decimal place would be able to distinguish between the two compounds. Most high-resolution mass spectrometers, however, are much more accurate than that, and many are accurate to the fourth decimal place.

Changing the Weight: Isotopes



Because mass spectrometry determines the weights of fragments, atoms that naturally have heavy isotopes become important.

Isotopes are atoms that have the same number of protons and electrons, but different numbers of neutrons.

Isotope effects are most readily observed in compounds containing the halogens chlorine (Cl) and bromine (Br). In nature, chlorine consists of about 75 percent of the ^{35}Cl isotope and about 25 percent of the heavier ^{37}Cl isotope, in which the chlorine has two additional neutrons. This means that if 100 chlorine-containing molecules were chosen at random, 75 of them would contain the ^{35}Cl isotope, while 25 of them would weigh two mass units more because they contain the heavier ^{37}Cl isotope. Because mass spectrometry weighs molecules, these heavier-mass isotopes will be observed in the mass spectrum.

In fact, both of these isotopes will be seen in the mass spectrum. But because a sample of a chlorine-containing molecule has three times as many of the ^{35}Cl isotope as it has of the heavier ^{37}Cl isotope, the molecular ion peak (which corresponds to molecules containing the ^{35}Cl isotope) will be three times as intense as the peak two mass units heavier that corresponds to molecules containing the heavier isotope. Because this heavy isotope peak is two mass units heavier than the ^{35}Cl isotope, it's called the M+2 ion. (If the heavy isotope is heavier by one neutron, it's called the M+1 isotope peak; by two neutrons, the M+2 peak; by 3 neutrons, the M+3, and so on.)

These isotope effects allow you to spot molecules that contain chlorine, because the spectra of a chlorine-containing molecule will contain a peak that's two mass units heavier than the molecular ion (M+) and that's one-third as intense as the M+ peak (see Figure 14-6).

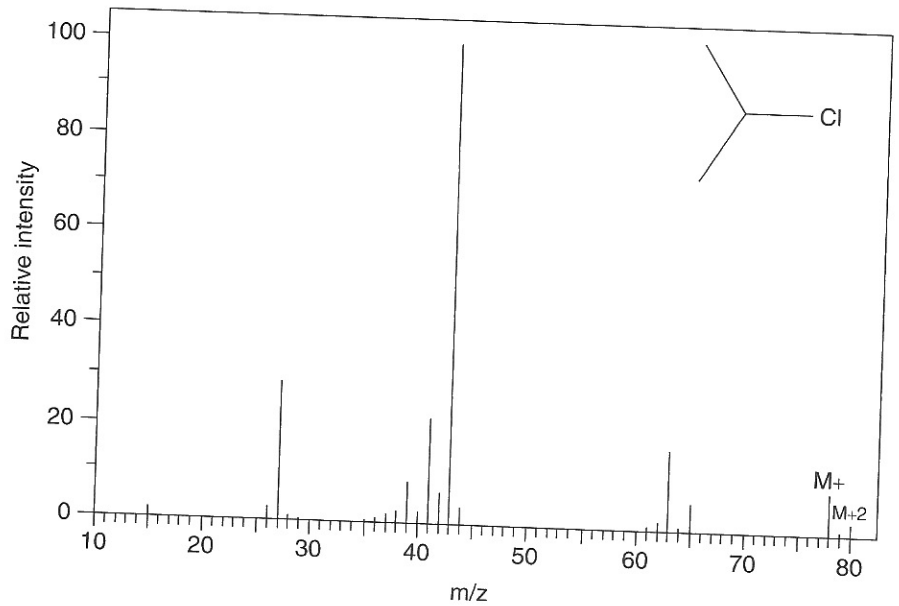


Figure 14-6: The mass spectrum for 2-chloro-propane (C_3H_7Cl).

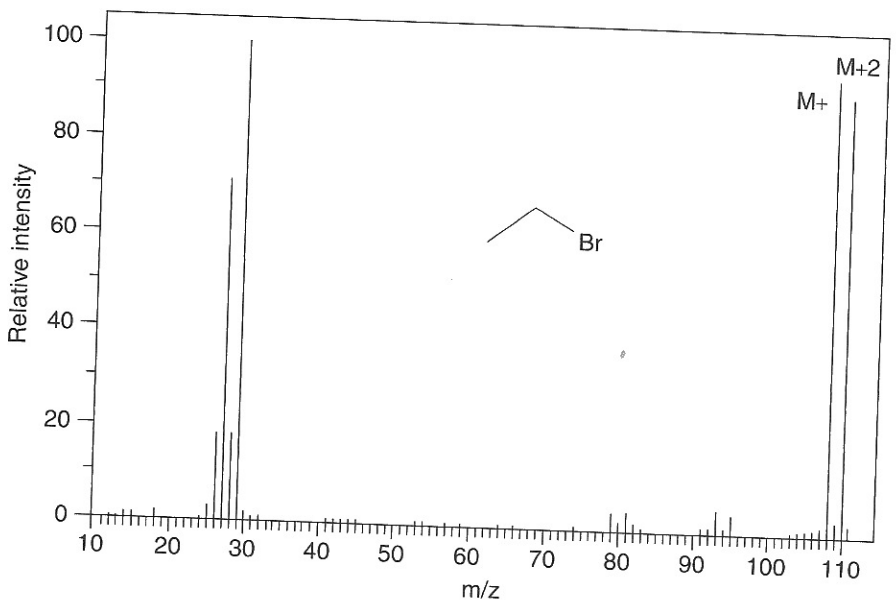


Figure 14-7: The mass spectrum for ethyl bromide (C_2H_5Br).

Other atoms have isotopes that are less abundant. Naturally occurring carbon contains about 1 percent of the ^{13}C isotope. Because a molecule that consists of many carbons will have a greater chance of having a ^{13}C atom, molecules with many carbon atoms will have a larger ^{13}C isotope peak in the mass spectrum than molecules that contain fewer carbon atoms. (Because ^{13}C is one mass unit heavier than ^{12}C, the isotope peak is called the M+1 peak.) This, in fact, is a crude way to determine the number of carbons in the molecule, because the size of the M+1 isotope peak relative to the molecular ion (M+) peak depends on the number of carbons in the molecule.

The Nitrogen Rule

Any molecule that contains only carbon, hydrogen, oxygen, or the halogens (F, Cl, Br, I), will have an even-numbered molecular weight. However, molecules that contain an odd number of nitrogens will have odd molecular weights. Knowing this, you can spot certain molecules that contain nitrogen, because if your molecular ion (M+) peak occurs at an odd-numbered *m/z* value, the molecule must contain an odd number of nitrogens. This is because nitrogen has three bonds and a lone pair of electrons, rather than four bonds like carbon (thus, for every nitrogen you substitute for carbon, you lose one hydrogen). An even number of nitrogens will lead to an even-numbered molecular weight (Figure 14-8).

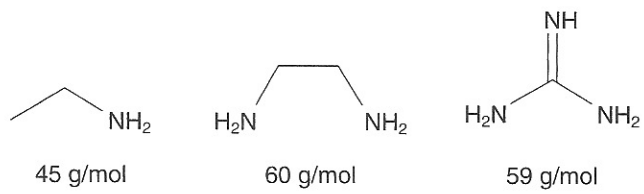


Figure 14-8: Seeing the nitrogen rule.

Identifying Common Fragmentation Patterns

Often, predicting what peaks will be observed in the mass spectrum is possible simply by looking at a structure and seeing which pieces would be easy to break off to make stable cations. In the following section, I go through some common structural features that make stable cations.



The ionizer makes the molecules into radical cations, which then generally break apart into a cationic piece (which is seen by the detector) plus a neutral radical piece (not seen by the detector).

Smashing alkanes

Alkanes generally break apart to make the most highly substituted cation. Tertiary cations (cations substituted with three carbons) are more stable than secondary cations (cations substituted with two carbons), which in turn are more stable than primary cations (cations substituted with only one carbon). Therefore, breaks in a molecule that make tertiary cations are likely to give fragments that correspond to large peaks in the mass spectrum, because the most stable fragments produce the largest peaks. See Figure 14-9.

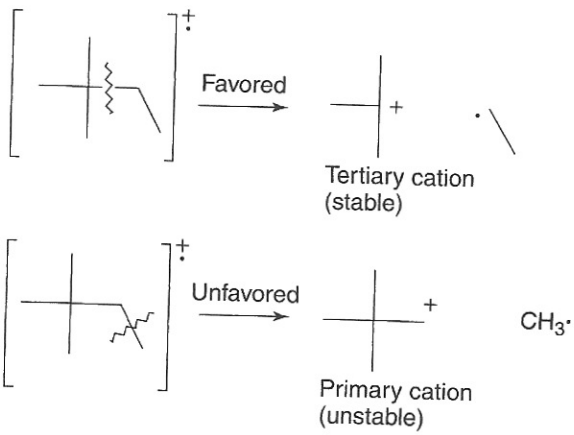


Figure 14-9: Favored and unfavored bond cleavage.

Breaking next to a heteroatom: Alpha cleavage

When a molecule contains heteroatoms (elements such as oxygen, sulfur, and nitrogen), breaking next to these atoms makes cations that are resonance stabilized. For example, breaking the C-C bond next to an alcohol group creates a resonance-stabilized carbocation. This type of break is called *alpha cleavage*, and is commonly seen in alcohols (as shown in Figure 14-10).

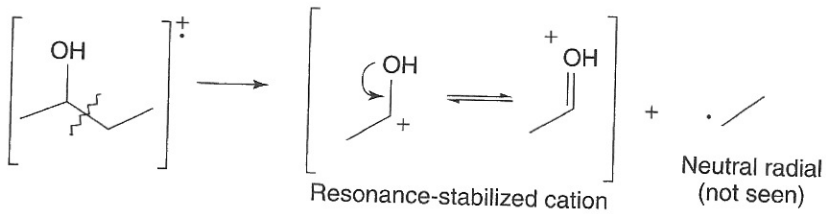


Figure 14-10: Alcohol alpha cleavage.

This same pattern of alpha cleavage is observed with amines, as shown in Figure 14-11.

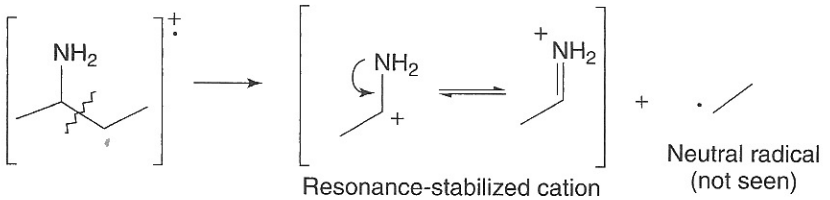


Figure 14-11: Amine alpha cleavage.

Alpha cleavage is also commonly seen in ethers, where the bond breaks adjacent to the oxygen. See Figure 14-12.

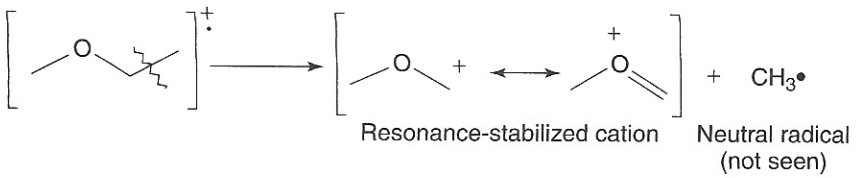


Figure 14-12: Ether alpha cleavage.

Breaks are often seen next to carbonyl groups (C=O groups), because this creates the resonance-stabilized cation. (I hope this is getting repetitious.) See Figure 14-13.

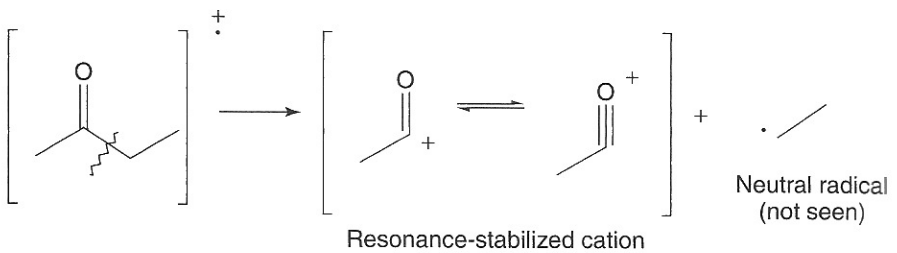


Figure 14-13: Carbonyl alpha cleavage.

Loss of water: Alcohols

In addition to alpha cleavage, alcohols readily lose a water molecule to form an alkene (a carbon-carbon double bond). This is why the mass spectrum of an alcohol often has a peak corresponding to the loss of eighteen mass units (the weight of water). See Figure 14-14.

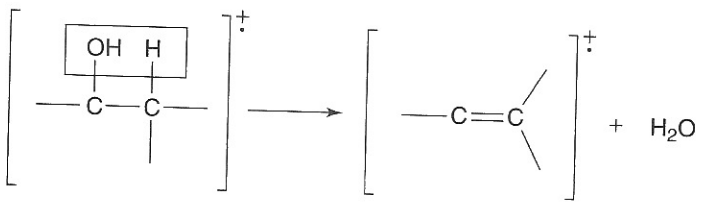


Figure 14-14: Alcohol dehydration.

Rearranging carbonyls: McLafferty Rearrangement

Some radical cations can also rearrange. The most famous rearrangement is called the *McLafferty Rearrangement,* which can occur on carbonyl compounds (such as ketones and aldehydes; see Chapter 5 for more on carbonyl functional groups) that have a hydrogen on a carbon that's three carbons away from the carbonyl group. This third carbon position is called the gamma, or γ, position. The rearrangement involves a six-membered ring transition state in which the carbonyl group pulls off the γ proton, breaking the molecule into two pieces. These pieces consist of an enol radical cation (recall that an enol is a combination of an alk*ene* and an alcoh*ol*) and a neutral alkene fragment (a fragment with a carbon double bond). The enol radical cation is observed in the mass spectrum, while the neutral alkene fragment is not observed. Any carbonyl compound that has a hydrogen in the γ position is likely to have a peak in the mass spectrum corresponding to the enol radical cation that's formed by the McLafferty Rearrangement of that carbonyl compound. An example of the McLafferty Rearrangement is shown in Figure 14-15.

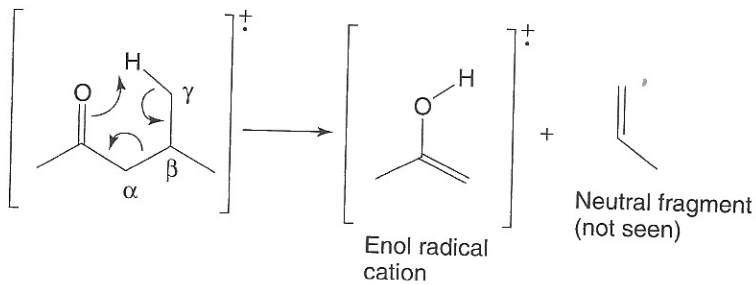


Figure 14-15: McLafferty Rearrangement.

Breaking benzenes and double bonds

Breaking one carbon away from an aromatic ring leads to the stable benzylic cation as shown in Figure 14-16. This benzene ring stabilizes the cation through resonance (see Chapter 3).

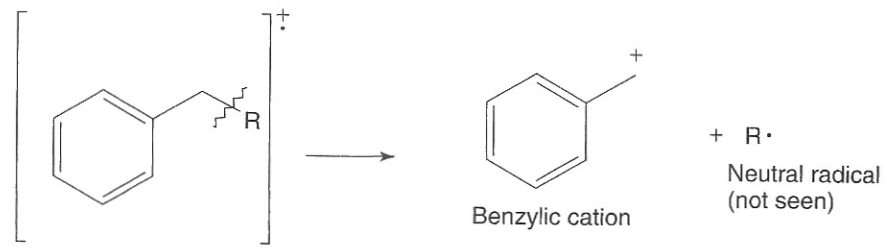


Figure 14-16: Benzylic cleavage.

Likewise, breaking the bond one carbon away from a double bond leads to an allylic cation that's stabilized by resonance. Note that breaking adjacent to the double bond leads to the unstable vinylic cation, as shown in Figure 14-17.

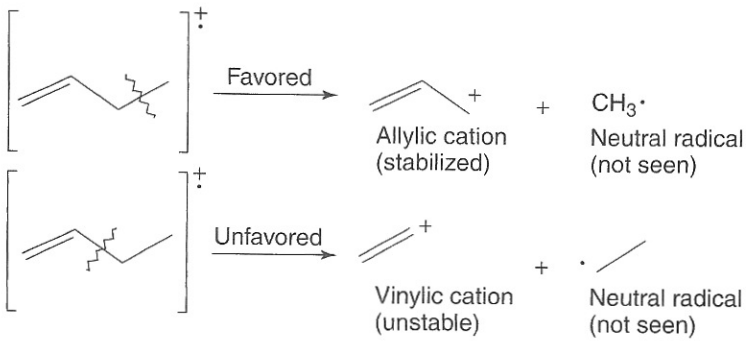


Figure 14-17: Fragmentation next to alkenes.



The loss of 15 mass units from the molecular ion generally indicates a loss of a methyl (CH_3) group. The loss of 29 mass units often indicates loss of an ethyl (CH_2CH_3) group.

Self test: Working the problem

Here's a sample question of the type you may see on an exam: The mass spectrum for 2-pentanone is shown in Figure 14-18. Draw the fragments responsible for the peaks in the mass spectrum at *m/z* 86, 71, 58, 43.

The main piece of information to remember in answering these types of questions is that each of the structures you draw *must be positively charged.* Neutral fragments are discarded and don't reach the detector.

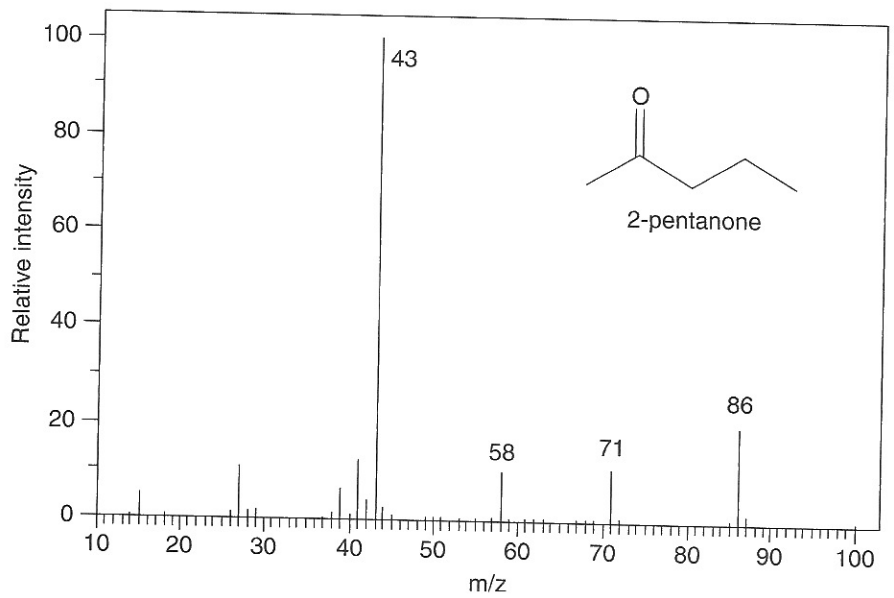


Figure 14-18: Mass spectrum for 2-pentanone ($C_5H_{10}O$).

Usually the best way to start is by looking for likely breaks in the molecule. Can you get an alpha cleavage (a break next to a heteroatom like O or N)? Can the molecule break to form a benzylic fragment or allylic fragment? Can a tertiary cation be made? If it's a carbonyl compound, does it have a gamma hydrogen that could be involved in a McLafferty Rearrangement?

This example has neither a benzene ring nor a carbon-carbon double bond. It doesn't have the capacity to make a tertiary cation, either. But it does have a heteroatom (oxygen). So, alpha cleavage would definitely be a possibility. Additionally, because it's a carbonyl compound and has a hydrogen in the gamma position, you'll probably see a peak for the McLafferty Rearrangement.

Start with alpha cleavage. The molecule can split on the left of the carbonyl group to make the resonance-stabilized cation that has a molecular weight of 71 g/mol. You may have already noticed that this peak with an *m/z* of 71 is fifteen mass units below the molecular ion peak, suggesting a loss of a methyl group. This cleavage is shown in Figure 14-19.

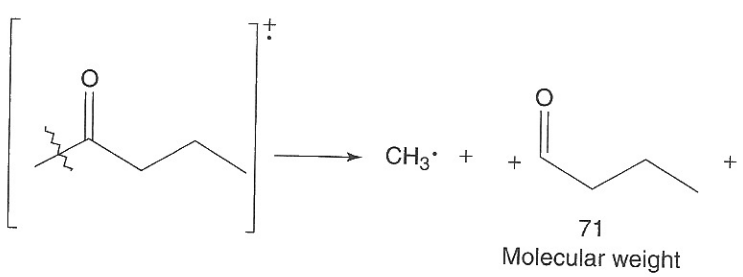


Figure 14-19: Alpha cleavage.

Or the molecule could split via an alpha cleavage on the right side of the carbonyl to make a cationic fragment that weighs 43 g/mol, as shown in Figure 14-20.

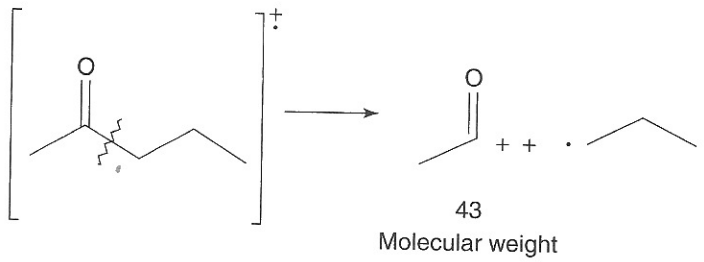


Figure 14-20: Another possible alpha cleavage.

Now try the McLafferty Rearrangement. I have redrawn the molecule to make it easier to see which bonds get made and which bonds get broken. The McLafferty Rearrangement gives the piece that weighs 58 g/mol, as shown in Figure 14-21.

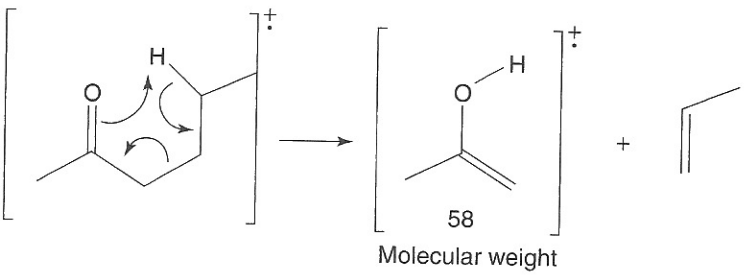


Figure 14-21: McLafferty Rearrangement.

Key Ideas Checklist

For mass spectrometry, there's a good bit of detail that you need to keep track of, so it's easy to lose sight of the big picture. But here's a list of the main ideas and uses of mass spectrometry.

- Mass spectrometry is very sensitive. Only miniscule amounts of material are required to do an analysis.
- Only positively charged fragments are observed in a mass spectrum.
- The weights of fragments are plotted versus the intensity (or relative number of fragments) on the spectrum. The highest intensity peak is arbitrarily assigned an intensity of 100.

- Atoms that have abundant heavy isotopes can often be spotted in a mass spectrum (particularly Cl and Br).
- Stable fragments (cations) have more intense peaks in the mass spectrum than do unstable fragments.
- The molecular formula of an unknown can often be determined using high-resolution mass spectrometers.

Chapter 15

Seeing Good Vibrations: IR Spectroscopy

In This Chapter

- Understanding how IR spectroscopy works
- Seeing the IR spectrum
- Identifying functional groups from IR spectra

Today, expert infrared (IR) spectroscopists are a lot like cowboys. It's not that these chemists are cool like cowboys, or that they can hold their liquor like cowboys, or that they can beat up a buncha roughnecks in a saloon like cowboys, or even that they can attract the opposite sex like cowboys. Come to think of it, in most ways expert IR spectroscopists are the complete opposites of cowboys. But, like cowboys, expert IR spectroscopists are something of a dyin' breed (insert soulful Country/Western dirge).

Over the past 30 years, the art of gleaning structural information from an IR spectrum has been slowly going the way of record players and LPs — which is to say that this art is reminisced about over snifters of brandy by old-timers when thinking about the way life was before such terrible modern contrivances as indoor plumbing, the polio vaccine, and NMR spectroscopy. Because before NMR spectroscopy became widespread, organic chemists were usually experienced enough in the art of IR spectroscopy to squeeze detailed structural features of an unknown compound from the pulp of an IR spectrum.

Today, though, most organic chemists just extract the juicy bits from an IR spectrum, and (when no one's looking) chuck the pulpy remains in a dustbin. Nowadays, organic chemists look at an IR spectrum primarily to see what functional groups are present in a particular molecule, and then use NMR spectroscopy (see Chapters 21 and 22) to determine the structural details of the molecule. (For a review of the main functional groups, turn to Chapter 6.)

But although IR spectroscopy is somewhat less powerful than NMR, IR is still very useful as a structure-analyzing tool, and is widely used by modern organic chemists. Because the IR spectrum of a molecule tells you what functional groups are present in that molecule, and because taking an IR spectrum is a cinch (spectra can often be obtained in less than a minute), IR spectroscopy gives you a lot of bang for your buck (timewise, I mean; IR spectrometers are still somewhat expensive).

In this chapter, I discuss how IR spectroscopy works. I show you how an IR spectrum is taken, and I discuss how you can analyze an IR spectrum to determine which of the major functional groups are present in a compound.

Bond Calisthenics: Infrared Absorption

It's easy to be fooled by fixed chemical structures and tables of precise bond lengths into thinking that bonds in molecules are fixed. But bonds are dynamic things. Bonds are not of fixed length, but instead are constantly stretching, bending, flexing, rotating, and rocking (and if a bond is a rockin', don't come a knockin'). So when you refer to a bond length as being x angstroms long, you're talking about an average length, not a fixed distance. In fact, bonds behave kind of like springs that are in constant motion (see Figure 15-1). If you stretch a bond too far, it will apply a restoring force, snapping back in the opposite direction just like a spring.

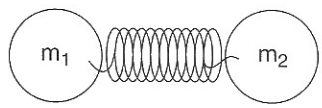


Figure 15-1: Bonds behave like springs.

Applying Hooke's law to molecules

Because bonds behave like springs, you can apply Hooke's law to determine the frequency of the vibrations of a bond (Hooke's law is used by physicists to describe the vibrations in springs). This frequency is described by the following equations, where v is the frequency, c is the speed of light, and k is a constant that indicates the spring's stiffness. The term μ is called the *reduced mass* and is a function of the masses of the two atoms involved in the bond (indicated by m_1 and m_2).

$$\upsilon = \frac{\pi c \sqrt{\frac{k}{\mu}}}{2} \qquad \mu = \frac{m_1 m_2}{m_1 + m_2}$$

The gist of these equations is that two main components determine the frequency of a bond motion. These components are:

- The masses of the atoms in the bond (which determine μ in the equations)
- The bond strength (or the spring constant, k)

Looking closely at this equation, you see that a spring attached to a light object will vibrate with higher frequency (higher υ) than a spring attached to a heavier object (because μ will be larger). Thus, a bond attached to a smaller atom (like hydrogen, say) will vibrate with higher frequency than a bond attached to a heavier atom (like carbon). Additionally, stronger springs (those with higher values of k) vibrate faster (that is, at higher frequencies) than weaker springs do, just as the stronger spring in a car suspension vibrates faster than a slinky when stretched and released. Translating this feature to molecules, triple bonds vibrate at higher frequencies than double bonds because triple bonds are stronger than double bonds. For the same reason, double bonds vibrate at higher frequencies than single bonds, because double bonds are stronger than single bonds.

Seeing bond vibration and IR light absorption

Many different motions are present in molecules — stretching motions, bending motions, twisting motions, and rocking motions. The most important motion for IR spectroscopy is stretching motions, as shown in Figure 15-2.

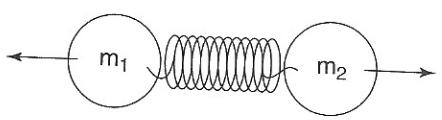


Figure 15-2: Stretching motion.

When a bond vibrates at a particular frequency (recall that this frequency is dictated by the weight of the two atoms and the strength of the bond), and light of that same frequency hits that bond, the light is absorbed by the molecule. This light absorption by the molecule can be detected. How? If you run

light of a particular frequency through the sample and more light goes into the sample than comes out, that frequency of light is being absorbed by the molecules, and thus one of the bonds in the molecule must vibrate at that frequency.

In practice, this measurement is performed by running one beam of light through a blank reference cell (typically, the reference cell is an empty sample holder if the sample is a solid or liquid, or a sample container with solvent if the sample is dissolved) and one beam through the sample, and then comparing the difference in the intensity of the light beam coming out of the sample cell with that coming out of the blank, as shown in Figure 15-3. A monochrometer is a device used in an IR spectrometer that can filter out all but the desired wavelength. To generate an IR spectrum, you scan the monochrometer through all the IR frequencies (which goes on the X axis) while simultaneously plotting the light transmittance on the Y axis. Even though, by convention, light transmittance (rather than light absorption) is plotted on the *y*-axis, peaks are usually referred to as absorptions, not transmittances!

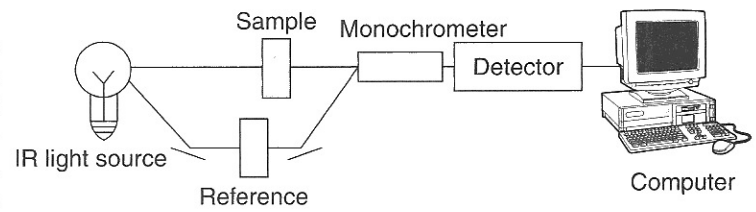


Figure 15-3: How an IR spectrometer works.

The frequencies of light required to excite the vibrations of bonds falls in — *surprise!* — the infrared region of the electromagnetic spectrum (slightly lower frequency than visible light). Hence the name "infrared spectroscopy."

Seeing absorption intensity

You now know that a bond will absorb light when it's hit with light that has the same frequency as the frequency of the bond vibration. But what about the intensity of the absorption? The intensity of the absorption of light depends on the change in the dipole moment (see Chapter 2) of a particular vibration (this absorption intensity relates to the way that electromagnetic radiation — that is, light — interacts with molecules). Bonds that have large changes in dipole moment for a particular vibration have intense light absorptions.

For example, consider the stretching vibrations for a C-H, N-H, and O-H bonds. Stretching an O-H bond produces a large change in dipole moment because

oxygen is much more electronegative than hydrogen (refer to Chapter 2 for an explanation of electronegativity). Nitrogen is a less electronegative atom than oxygen, and so N-H bonds have a smaller change in dipole moment when stretched than do O-H bonds. A C-H stretch has an even smaller change in dipole moment because carbon is not very electronegative at all. Thus, O-H stretches have intense light absorptions, N-H bonds have weaker absorptions, and C-H stretches are weaker still, as summarized in Figure 15-4.

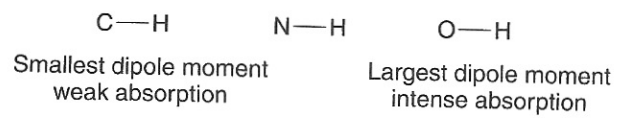


Figure 15-4: Absorption intensity of bonds.

IR forbidden stretches

If a bond motion produces no change in the bond's dipole moment, the vibration will not absorb light at all. The vibrations that produce no change in dipole moment are called *IR inactive vibrations,* because they will not show up in an IR spectrum. Typically, these IR inactive vibrations occur in symmetrical molecules, because stretching these molecules does not change the dipole moment of the bond. For example, stretching the Cl-Cl bond in chlorine, or stretching the carbon-carbon triple bond in dimethyl acetylene (shown in Figure 15-5), does not change the dipole moment. These stretch modes are thus IR inactive, and do not show up in the IR spectrum.

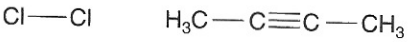


Figure 15-5: IR inactive bonds.

Dissecting an IR Spectrum

The IR spectrum is set up in a somewhat weird way. Instead of plotting absorbance, by convention the IR spectrum plots light transmittance. A zero value for transmittance indicates that none of the light passes through the sample at that wavelength (and thus all of the light is absorbed), and 100 percent transmittance indicates that all of the light passes through the sample at

that wavelength. To generate the IR spectrum, different frequencies of infrared light are passed through the sample, and the transmittance of light at each frequency is measured. The transmittance is then plotted versus the frequency of the light (which is presented in the somewhat unusual units of cm^{-1}).

Similar kinds of bonds show up in the same places in the IR spectrum, as Figure 15-6 shows. For example, the stretches associated with an alcohol (a molecule containing an OH functional group) show up generally in the same region of the spectrum regardless of what the rest of the molecule looks like.

Note how Figure 15-6 makes sense in terms of the two factors that contribute to the vibration frequency — the size of the atom and the bond strength. Absorptions at high frequency (like those produced by OH, NH, and CH) appear at higher frequency than the absorptions produced by C-C bonds (including single, double, and triple carbon-carbon bonds) because hydrogen is a smaller atom than carbon. Also, triple bonds absorb at higher frequency than double bonds because triple bonds are stronger than double bonds.

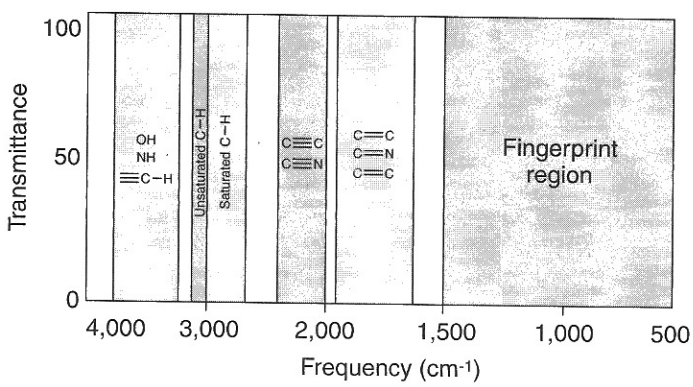


Figure 15-6: Typical bond absorption locations.

The region of the spectrum between 500 cm^{-1} and 1500 cm^{-1} is called the fingerprint region (refer to Figure 15-6). Every molecule has a unique set of absorptions in the fingerprint region of the spectrum. Unfortunately, this region of the spectrum is usually a complicated mess and is difficult to interpret. For this reason, beginners in the art of interpreting IR spectra typically ignore this region of the spectrum. However, the fingerprint region can still be useful for identifying unknown compounds, because two molecules that have identical fingerprint regions in the IR spectrum are almost certainly identical molecules. Thus, finding that the fingerprint region of your unknown compound's IR spectrum and that of a known reference are identical is good evidence that the structure of the unknown is the same as the reference.

Identifying the Functional Groups

Table 15-1 lists the locations and intensities of absorptions produced by typical functional groups. Recognizing where the absorptions generated by the common functional groups occur will help you to interpret IR spectra.

Table 15-1 IR Absorptions of Common Functional Groups

Functional Group	*Absorption Location (cm^{-1})*	*Absorption Intensity*
Alkane (C–H)	2,850–2,975	Medium to strong
Alcohol (O–H)	3,400–3,700	Strong, broad
Alkene (C=C)	1,640–1,680	Weak to medium
(C=C–H)	3,020–3,100	Medium
Alkyne		
(C≡C)	2,100–2,250	Medium
(C≡C–H)	3,300	Strong
Nitrile (C≡N)	2,200–2,250	Medium
Aromatics	1,650–2,000	Weak
Amines (N–H)	3,300–3,350	Medium
Carbonyls (C=O):		Strong
aldehyde (CHO)	1,720–1,740	
ketone (RCOR)	1,715	
ester (RCOOR)	1,735–1,750	
acid (RCOOH)	1,700–1,725	

Sizing up the IR spectrum

The IR spectrum of hexane (C_6H_{14}) is shown in Figure 15-7. Because hexane has only C-H and C-C bonds (and no functional groups), this spectrum can help orient you to the important regions in an IR spectrum.

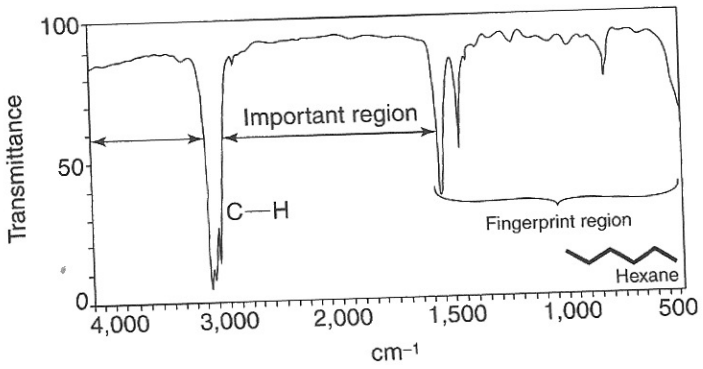


Figure 15-7: The IR spectrum of hexane.

Note the two features of the spectrum — the C-H absorptions between 2,800 cm^{-1} to 3,000 cm^{-1}, and the fingerprint region below 1,500 cm^{-1}. You should think of this spectrum as a blank; you mentally subtract out the two regions shown on this spectrum to look for the important absorptions in unknown compounds. Using these C-H stretches as a frame of reference is also convenient, because almost every organic compound contains C-H bonds. (Note that while individual C-H stretches are weak because of small changes in the dipole moment, a typical molecule often has a lot of these bonds, which makes these absorptions appear fairly intense). Any absorptions to the left of these C-H stretches are typically N-H,O-H, or alkynyl (triple bond) C-H stretches. The other common functional groups have bands between the fingerprint region and the C-H stretching absorptions.



Don't get too distracted by the mess in the fingerprint region. Instead, look primarily in the important places (between 1,500 and 2,800 cm^{-1}, and above 3,000 cm^{-1}.

Recognizing functional groups

Memorizing where the functional groups appear in the spectrum is usually not enough. You need to be able to recognize and get a feel for what the absorptions of the common functional groups look like. Are they fat and round like a sumo wrestler's belly (as in an O-H stretch), or are they small and thin (like a carbon-carbon double bond stretch)? In Figure 15-8, I show you what the common functional groups look like.

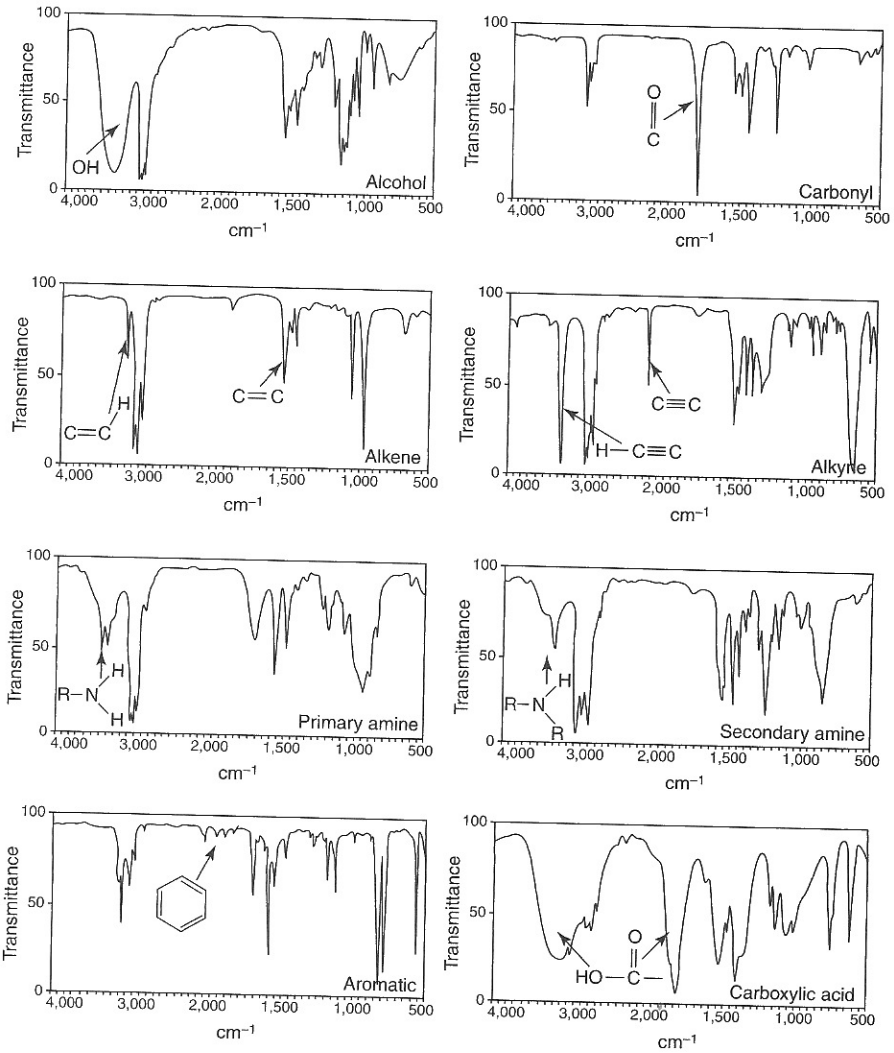


Figure 15-8: Absorptions of different functional groups.

Seeing to the Left of the C-H Absorptions

Look left and then right. In this section, I cover the features of the functional groups that appear to the left of the C-H absorptions in the IR spectrum. Refer to Figure 15-8 for examples of these functional groups.

Big and fat: The alcohols

Alcohols are very broad, fat absorptions that come to the left of the C-H absorptions. Because of their broadness, they're very easy to spot.

Milking the spectrum: Amines

Primary amines (amines substituted by only one R group and abbreviated RNH_2) are very easy to spot. They appear to the left of the C-H absorptions in the spectrum in about the same region as alcohol absorptions. Primary amines consist of two small peaks, and the overall effect is to make the absorptions of a primary amine look like a cow udder (refer to Figure 15-8). Secondary amines (amines substituted by two R groups and abbreviated R_2NH) consist of only a single absorption in that region. A common mistake is to confuse secondary amine absorption with alcohol absorptions, because they both occur in the same region of the spectrum. Usually, secondary amine absorptions are somewhat thinner and sharper than the broad and rounded absorptions produced by alcohols. Only practice with problems dealing with IR spectra will make you confident in telling the difference between amine and alcohol absorptions.

Seeing to the Right of the C–H Absorptions

I now cover the features of the functional groups that appear to the right of the C-H absorptions in the IR spectrum but to the left of the fingerprint region.

Big and tall: Carbonyl groups

Carbonyl groups are very easy to spot in an IR spectrum. They consist of an intense, thin absorption at about 1,700 cm^{-1} that looks like a finger (not a middle finger, I hope). Conjugated carbonyls (carbonyl groups adjacent to double bonds) have a somewhat lower frequency of vibration than ketones (these conjugated carbonyls often have absorptions below 1,700 cm^{-1}). Ester carbonyls have a somewhat higher frequency of vibration than ketones. A carboxylic acid has a very fat carbonyl stretch and an alcohol absorption that's even fatter than a typical alcohol stretch; this alcohol stretch from the carboxylic acid often expands into the region of the C-H stretches.

Hydrocarbon stretches: Alkenes, alkynes, and aromatics

Alkene (C=C) stretches appear around 2,250 cm^{-1}, and are of either weak or medium intensity. If you're unsure whether a small blip in that region of the spectrum represents an alkene, you can look for the unsaturated hydrogen stretches (C=C-H) above 3,000 cm^{-1}. Typically, these are of medium intensity. Drawing a line down the spectrum at 3,000 cm^{-1} is often a good idea. Any stretches slightly higher than that frequency are a good indication of having an alkene (or an aromatic ring). Alkynes (carbon-carbon triple bonds) have absorptions between 2,100—2,250 cm^{-1}, and are of medium intensity. A terminal alkyne (one at the end of a chain) is easy to spot because of the high intensity alkynyl C-H stretch that comes at around 3,300 cm^{-1}. Aromatic ring absorptions, on the other hand, can be tough to spot sometimes. They consist of a small series of bumps between 1,650 cm^{-1} and 2,000 cm^{-1}. The number of bumps (absorptions) changes depending on how the benzene ring is substituted.

Chapter 16

NMR Spectroscopy: Hold on to Your Hats, You're Going Nuclear!

In This Chapter

- Discovering the power of NMR spectroscopy
- Understanding chemical equivalency and symmetry
- Examining an NMR spectrum
- Seeing ^{13}C NMR
- Combining integration and coupling

Imagining modern organic chemistry without the aid of Nuclear Magnetic Resonance spectroscopy (NMR) is a lot like imagining modern life without the aid of cars or toilet paper: virtually unthinkable. That's because if one of the chief purposes of organic chemistry is to figure out ways to make carbon-containing stuff, then that process becomes a lot easier if you can determine what it is that you've made. And that's what NMR is for — it can help you to determine the precise molecular structure of whatever organic stuff you're interested in looking at. This stuff might include the products of reactions, an interesting metabolite that you've just isolated from rabbit muscle, a deadly neurotoxin that you've extracted from a marine shellfish, or just about anything else, really.

In this chapter, I explain the value of NMR, discuss how it works, and explain how NMR experiments are run. I also dissect the different pieces of an NMR spectrum, show you how all the different parts can give clues about a compound's structure, and discuss what each part means. In Chapter 17, I show you how to determine the structure of an unknown molecule using NMR spectroscopy.

Why NMR?

Back in the old days when NMR spectroscopy was still in its infancy (and people had to walk five miles to get to school, uphill both ways), chemists had to labor sometimes for weeks to figure out the structures of even simple organic compounds, using methods that were tedious, time-consuming, and about as reliable as a fox guarding a hencoop. For example, a chemist might have compared *the physical properties of a compound — its boiling point, melting point, refractive index, and so on — to compounds of similar* structure previously reported in the literature to see if any of the known compounds were close matches. But because of the millions of possible structures, often the published literature contained no compounds of similar structure, so the molecule would need to be converted into a known derivative, and then the properties of this derivative would be tested.

Suffice it to say this method of structure determination was wearisome, unreliable, and about as fun as a root canal. But much to the delight of chemists today (and perhaps to the chagrin of the struggling organic student), NMR spectroscopy has now swaggered onto the scene. Hydrogen NMR can often be used to determine the structure of simple unknown compounds within minutes, eliminating most of the tiresome hassle figuring out the structures of molecules. You just pop your sample in the NMR spectrometer, run the experiment on the quick, and print out your data. Just like that — one, two, three — and you're off to the analysis, as quickly as a politician to promise a tax cut.

Couple NMR's speed with its ability to determine structure, and you've got a tool that's amazingly powerful, a tool that can nail down the structure of almost any organic molecule, from the relatively small and simple molecules like the ones that you encounter in your organic course, to the large and staggeringly complex ones like the massive enzymes that catalyze chemical reactions in the cell. Because of NMR's power and versatility, when organic chemists want to figure out exactly what that foul-smelling product from their reaction is, they turn to NMR to give them the definitive answer.

So while mass spectrometry (see Chapter 14) can give you information about the molecular weight of a compound (and if you're good, perhaps some its structure), and IR spectroscopy (see Chapter 15) can give you an idea of what kinds of functional groups a molecule may have, only NMR can show you reliably how a molecule is pieced together. Don't take this the wrong way: Mass spectrometry and IR spectroscopy are often integral pieces of structure determination, and they both provide first-class clues. But NMR is the Bad, Bad Leroy Brown of molecule identification. If figuring out a structure can be thought of as a chess game, then NMR spectroscopy has the moves of the queen: It's the most powerful piece on the board.

How NMR Works

NMR works by allowing you to "see" the nuclei in a molecule, and to see the chemical neighborhood of those nuclei. Knowing the chemical environment and the number of different kinds of nuclei present allows you to piece together the structure of a compound in most circumstances. Some nuclei, however, are *NMR active,* and some are *NMR inactive;* NMR experiments see only NMR active nuclei, and are blind to nuclei that are NMR inactive. Fortunately, both carbon and hydrogen nuclei are NMR active. For reasons I talk about in this chapter, hydrogen NMR (often called proton NMR or ^{1}H NMR) is often the most useful NMR type for organic chemists; therefore, all discussions will pertain to hydrogen NMR. After I cover hydrogen NMR, I cover the main points of ^{13}C NMR (which is pretty much the same thing as hydrogen NMR, only simpler).

Giant magnets and molecules: NMR theory

The theory behind NMR spectroscopy can be complicated — and the details are generally outside the scope of a general organic class — so the following discussion is a simplified version of how NMR works. Even simplified, it's complicated, so buckle up and fasten your thinking caps.

All nuclei with odd atomic and mass numbers have the property of spin just as electrons do, and any nucleus that has spin is observable by NMR. *Spin* is a bit of an abstract concept that doesn't really have any counterpart outside of the subatomic world, but it might be helpful to think of these spins as coming from the protons spinning rapidly inside the nucleus, or the equivalent of a positive charge break dance. This spinning involves the movement of a positive charge; according to the laws of physics, the movement of charged particles creates a magnetic field with a *magnetic moment.* Nuclei that have such spins include ^{1}H, ^{13}C, ^{15}N, ^{19}F, because all of these elements these have odd atomic numbers. Nuclei with even atomic numbers like ^{16}O, ^{12}C, and ^{14}N, are NMR inactive, and will not show up in an NMR experiment.

The magnetic moments that come from the nuclear spins have direction. If you were to simply take a beaker full of nuclei and place it on a tabletop in your kitchen, the directions of the magnetic moments from the nuclei would be random, pointing in every possible direction. But when the nuclei are placed between the poles of a magnet — which creates what is called the *external magnetic field* — quantum mechanics dictates that the direction of the magnetic moments of these nuclei must either line up with the external magnetic field (called an α spin) or line up against it (called a β spin). You can imagine the magnet shouting a sort of politician's rallying cry to the nuclei, "Everyone take sides; you're either with me or you're against me." Thus, nuclei in the same beaker can line up with or against the magnet (see Figure 16-1).

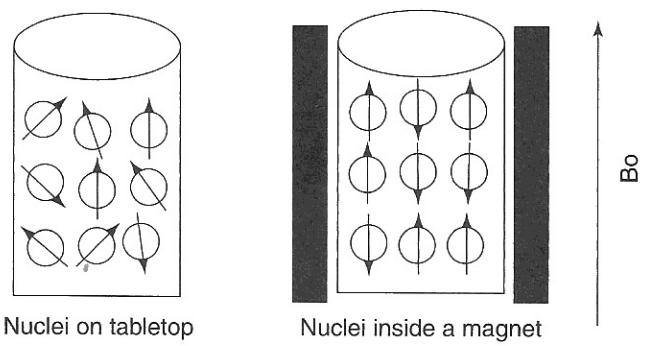


Figure 16-1: The effect of an external magnetic field on the direction of the magnetic moments of individual nuclei.

Those nuclei that align with the magnetic field are slightly lower in energy than those that align against the magnetic field. How much lower in energy these nuclei are depends on the size of the magnet that you put near the nuclei. (This magnet size — or external magnetic field strength — is often labeled B_o.) As the size of the magnet increases, the difference in energy (ΔE) between the spins aligning with the magnetic field (α) and those going against the magnetic field (β) also increases (see Figure 16-2). This energy gap between the two kinds of spins is what an NMR experiment measures. The size of the energy gap tells you about the chemical neighborhood of particular nuclei.

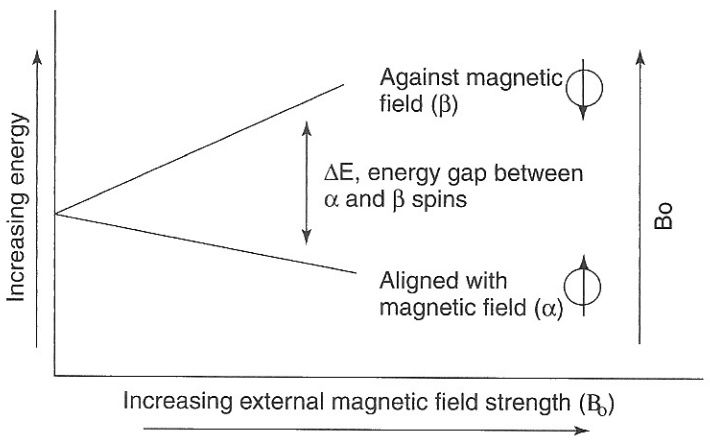


Figure 16-2: The effect of increasing external magnetic field strength (B_o) on the energy gap between α and β spin states.

But before I can talk about how the size of the energy gap between α and β spins gives you information about the chemical environment of the nuclei, I need to tell you first *how* the energy gap is measured by an NMR spectrometer.

Like most types of spectroscopy, NMR uses light to effect a transition between energy levels. (For IR spectroscopy, infrared light is used to transition between vibrational and rotational energy levels. See Chapter 15 for more on IR spectroscopy.) In an NMR experiment, a radio wave (which indicates light of radio frequencies) effects a transition between the α and the β spin energy levels. When the frequency of the radiowave that hits the sample has the exact energy of the energy gap between the α and β spins (ΔE), the light is absorbed by the nuclei.

The energy from the light absorption is used as a kind of nuclear spatula to flip the α spins into β spins, a process called *spin flipping*. When a nucleus absorbs light and flips its spin, the nucleus is said to be *in resonance* (which is where the term Nuclear Magnetic Resonance comes from; this resonance is not to be confused with resonance structures). A detector can measure the frequency of this absorption and plot it on a spectrum (which is the plot of an NMR experiment, which shows the intensity of the absorption versus the frequency). See Figure 16-3 for a diagram of how this works. A high frequency light absorption indicates a large energy gap between the α and β states; a low frequency light absorption indicates a small energy gap.

To sum up, the ΔE in an NMR experiment is determined in the following way:

- The sample is placed inside a huge magnet (called the external magnetic field, or B_o).
- The direction of the magnetic moments of the nuclei line up either with the external magnetic field (an α spin) or against it (a β spin). The energy difference between an α spin and a β spin is the ΔE.
- Upon absorption of light that has energy equal to the energy gap (ΔE), the nuclei come into resonance, and α spins are flipped into β spins.
- A detector measures the frequency of the absorbed light (which is proportional to the energy gap between the α and β spins) and then plots the frequency of the light absorbed on the NMR spectrum versus the intensity of light absorption.

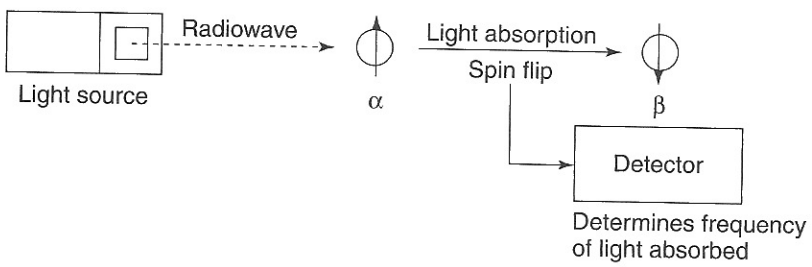


Figure 16-3: Diagram of the steps involved in measuring the ΔE in an NMR experiment.

So that's how an NMR spectrometer determines the energy gap. But if NMR only measured the energy gaps, then NMR would be about as useful to organic chemists as organic chemistry is to an economics major. In this simple scenario, all of the hydrogen nuclei would have the same energy gap between α and β, and the NMR spectrum would only show a single peak (or single light absorption), representing all of the hydrogens in the molecule. And that wouldn't be particularly helpful. But my discussion so far has omitted one key ingredient — electrons! So far, this discussion has been limited to bare nuclei that have no electrons surrounding them.

Grab your jackets: Electron shielding

Because they are moving charges, electrons have their own magnetic fields that come into play. The magnetic field of an electron opposes the external magnetic field (made by the big magnet that you placed the sample into) and shields the nucleus from feeling the full brunt of the external magnetic field. In other words, a naked nucleus feels more of the external magnetic field than does a nucleus that has electrons surrounding it, just as a nudist will feel more of the cold than a person wearing an insulating jacket.

Consequently, a nucleus that's jacketed with electron density shielding it from the external magnetic field will require a lower frequency (lower energy) radio wave to flip its spin than a nucleus that has less electron density around it. This is because the actual magnetic field that an electron-surrounded nucleus feels is smaller than the magnetic field felt by a naked nucleus, so the gap between the α and β spins is smaller (refer to Figure 16-2). Because the gap is smaller, less energy (lower frequency light) is required to flip the spin.

In this way, the chemical environment of the hydrogen nuclei is revealed. A hydrogen that's next to a highly electronegative element (see Chapter 2 for a discussion of electronegativity) will have fewer electrons around it and will therefore come into resonance — or will flip its spin — at a higher frequency of light. A hydrogen that's next to an electron-donating element will have lots of electrons around it, and will come into resonance at a lower frequency.

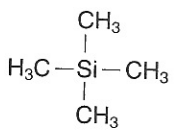
The NMR Spectrum

An NMR spectrum, then, is the plot of the resonance frequency versus intensity of light absorption. One way to take an NMR spectrum is to hold the external magnetic field constant (the magnetic field created by the big magnet) and

vary the frequency of the radiowaves shone onto the sample. At whatever frequencies light is absorbed, peaks are plotted on the spectrum. This is in fact how old NMR spectrometers plotted an NMR spectrum, and is a conceptually useful way of thinking about how an NMR spectrum is generated. The workings of a modern NMR spectrometer are a bit more complicated, but the general principle remains the same.

Standardizing chemical shifts

One potential problem for NMR is that if the nuclei are placed into a large magnet, their resonance frequency will be larger than when they are placed into a little magnet, because the energy gap increases as the external magnetic field increases (refer to Figure 16-2). This means that a proton will show up at a different frequency for the poor person who can only afford a small magnet than it will for a rich person who can afford a big magnet. To make the NMR spectrum the same for a given molecule regardless of how large the magnet is, the resonance frequency is plotted relative to a reference compound, usually tetramethylsilane (TMS), shown in Figure 16-4. This way, regardless of how big the external magnetic field is, the peaks in the NMR spectrum will always occur at the same location relative to TMS.



Tetramethylsilane (TMS)

Figure 16-4: Tetramethylsilane (TMS).

TMS is used as a reference because the hydrogens on the molecule are highly shielded because of the electron-donating silicon atom, and these hydrogens show up at a lower frequency than the vast majority of hydrogens in organic molecules. This TMS absorption frequency is arbitrarily assigned a value of zero on the spectrum. The frequency of a nucleus' absorption relative to TMS is given in units of parts per million (ppm), so that the frequency will be given in small, manageable numbers (between 0 and 15) rather than large numbers (0–15 million). For a hydrogen NMR spectrum, peaks generally fall between 0 and 15 ppm, with a peak close to 0 ppm indicating a highly *shielded* hydrogen (electron rich), and a peak close to 15 ppm indicating a highly *deshielded* hydrogen (electron poor). Figure 16-5 shows a hypothetical NMR spectrum.

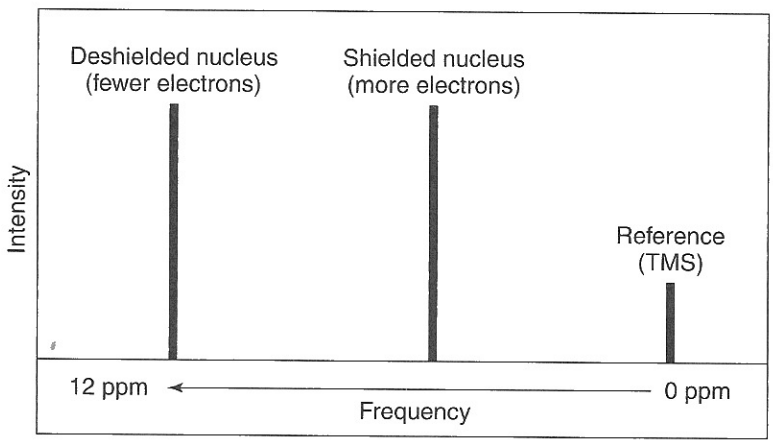


Figure 16-5: The NMR spectrum.

Seeing symmetry and chemical equivalency

Every hydrogen in a molecule that's in a unique chemical neighborhood will show up as a peak on an NMR spectrum. Two (or more) hydrogens that have equivalent chemical neighborhoods, though, will be represented by just a single peak. Such hydrogens that are in identical chemical environments are said to be *chemically equivalent.* For example, methanol (Figure 16-6) has four hydrogens in it, so you might expect it to show four peaks in the ^{1}H NMR spectrum, one for each hydrogen. But it only shows two peaks. This is because there are only two different kinds of hydrogens in methanol. Each of the hydrogens in the methyl group (CH_3) are in identical chemical environments — all three are attached to a carbon that's bonded to two other hydrogens and an alcohol group — and therefore each of these hydrogens sees the same chemical neighborhood. Therefore, all three hydrogens have the same resonance frequency and show up as a single peak. The second peak comes from the H on the alcohol (OH) group, which is in a different chemical environment.

Figure 16-6: Methanol.

H_3C — OH

Methanol

Butane (Figure 16-7) is another example of a molecule that has such chemical equivalency. Ten hydrogens are on the molecule, but, remembering the chemical equivalency of methanol, you might expect to see four peaks, one for each of the hydrogen sets attached to the carbons. But the NMR spectrum of butane has only two peaks. This is accounted for by a further element of equivalency

that comes from the symmetry of the molecule. Because the right-hand side of the molecule is exactly equal to the left-hand side, the two CH_3 groups on the ends are in identical chemical environments, as are the two CH_2 groups in the middle. Because both CH_3 groups are in identical chemical environments, and both CH_2 groups are in identical chemical environments, you only see two peaks in the NMR spectrum.

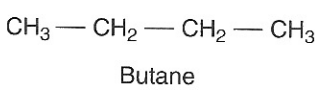


Figure 16-7: *Butane.*

Being able to recognize which hydrogens are chemically equivalent is extremely important. Generally, hydrogens attached to the same carbon are chemically equivalent. In addition, symmetry in the molecule can contribute further to chemical equivalency. You should practice looking at organic molecules for chemical equivalency so that you can determine how many peaks its ^1H NMR will have. See the "Seeing the chemical shift" section for details.



Often, drawing out all of the hydrogens on the molecule can help you see the different chemical environments each hydrogen experiences. Try this for the molecules shown in Figure 16-8.

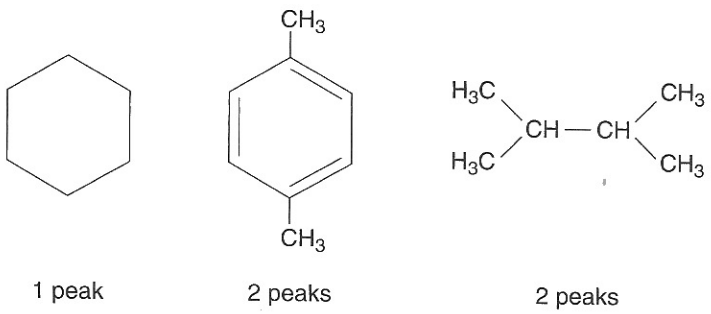


Figure 16-8: Seeing symmetry.

The NMR Spectrum Manual: Dissecting the Pieces

This section dissects each of the parts of an ^1H NMR spectrum and discusses how each part of a spectrum can give clues to help determine the structure of a molecule.

Seeing the chemical shift

Where a peak is located relative to the reference TMS is called its *chemical shift* (or its δ *value,* where δ indicates the absorption frequency and does not mean "partial" as used in Chapter 2 to indicate partial charges). The chemical shift is given in units of parts per million (ppm). The two most important factors that effect the chemical shift of a given nucleus are the electron density around a hydrogen and diamagnetic anisotropy (scary phrase, huh?).

A hydrogen neighboring highly electronegative atoms — like fluorine (F), chlorine (Cl), bromine (Br), nitrogen (N), and oxygen (O) — will have a higher chemical shift than a hydrogen neighboring more electropositive elements (like silicon [Si] or carbon [C]). The derivatives of methane shown in Figure 16-9 illustrate this point. As the electronegativity of the substituent increases (recall that electronegativity increases as you go from Br to Cl to F), the chemical shift also increases. This is because as the electronegativity of the substituent increases, the electron piggishness of the substituent also increases, and the substituent steals more of the electron density away from the hydrogens. Electron-deshielded nuclei like those near electronegative elements have a larger chemical shift than those near electropositive elements.

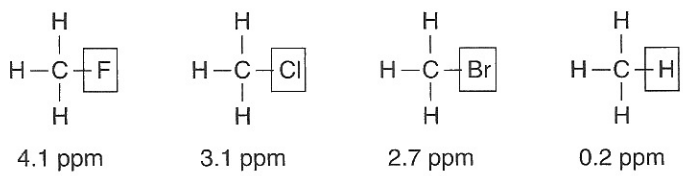


Figure 16-9: The chemical shifts of hydrogens (protons) caused by neighboring electronegative substituents.

The second effect on the chemical shift is a local field effects caused by pi electrons; this effect is called *diamagnetic anisotropy* in organic-speak.

When placed in a magnetic field, the pi electrons in benzene (or other aromatic rings) are induced to circulate. (For more on aromatic rings see Chapter 13. For information on pi bonds see Chapter 2.) This circulation of the pi electrons creates a local magnetic field from the aromatic ring (see Figure 16-10). Right on top or on the bottom of the aromatic ring the induced magnetic field from the

benzene opposes the external magnetic field, weakening it. Adjacent to the plane of the ring, however, the magnetic field of the benzene ring reinforces the external magnetic field, making the magnetic field stronger.

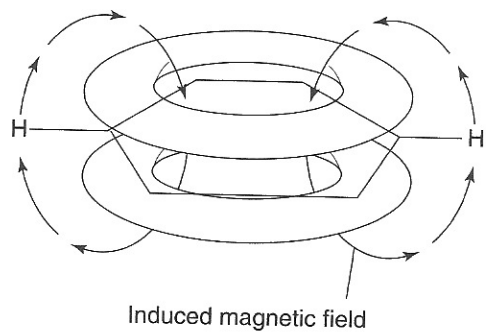


Figure 16-10: The induced magnetic field of benzene in an external magnetic field.

This means that any hydrogens directly above or below an aromatic ring will be shielded by the aromatic ring's magnetic field, and will have a lower chemical shift, while those hydrogens adjacent to the ring will be deshielded and will have a higher chemical shift. Therefore, hydrogens attached to aromatic rings (sometimes referred to as aromatic hydrogens, even though the hydrogens themselves are not aromatic), have a chemical shift much higher than you might expect based on the electronegativity considerations of the aromatic ring. Figure 16-11 illustrates this effect with a complex aromatic molecule.

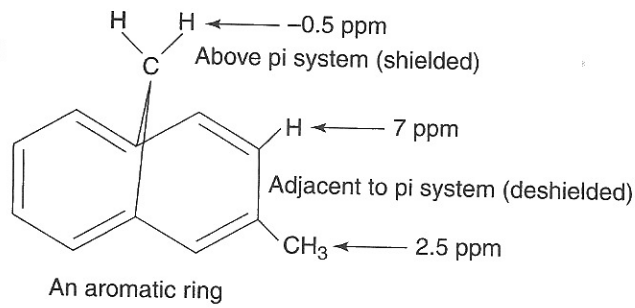


Figure 16-11: The effect of diamagnetic anisotropy in an aromatic molecule.

The same local field effect caused by the pi electrons in benzene affects double bonds and triple bonds in a similar fashion. Hydrogens attached to double bonds or triple bonds, therefore, have higher chemical shifts than might be expected based on simple electronegativity considerations.

Figure 16-12 shows some of the approximate chemical shifts of hydrogens adjacent to the common functional groups. Keep in mind, though, that these numbers are just typical ranges, and are not absolute; values may stray in an out of the ranges depending on the rest of the structure of a given molecule. Also keep in mind that the addition of electronegative elements is cumulative. A hydrogen adjacent to a carbonyl group plus a halide would have a chemical shift higher than a hydrogen neighboring just one of those groups.

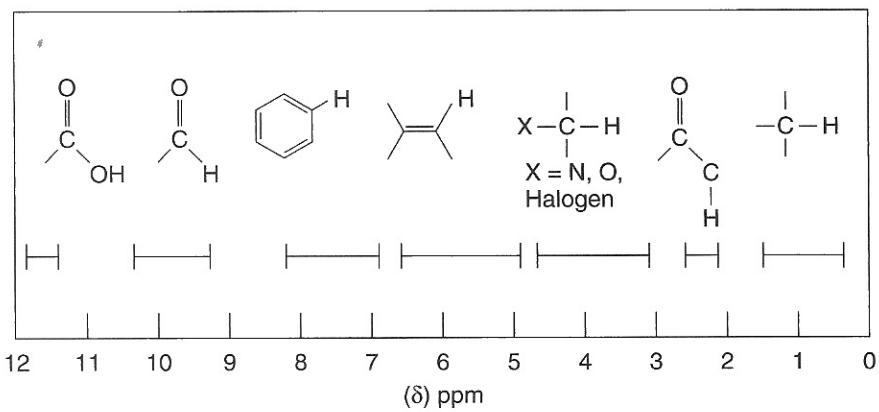


Figure 16-12: Approximate chemical shifts of hydrogens (protons) adjacent to the common functional groups.

Incorporating the integration

The peak intensity — or the area underneath a peak on a spectrum — is related to the number of hydrogens that that peak represents. A computer uses the mathematical process of integration to find the areas underneath each peak. The integration is shown on the spectrum by the addition of an integration curve (see Figure 16-13). The *height* of this integration curve is proportional to the area underneath a peak, and so this height is proportional to the number of hydrogens the peak represents. (The width of the curve is unimportant.)

To measure the height of an integration, you start at the bottom of the integration curve where it's flat, and measure to where the curve goes flat again. Unfortunately, integration cannot tell you how many hydrogens each peak represents, just the relative ratios of hydrogens in one type of chemical environment compared to those in another environment. This makes integration useful only for organic molecules that contain more than one kind of hydrogen (which, fortunately, is most of them).

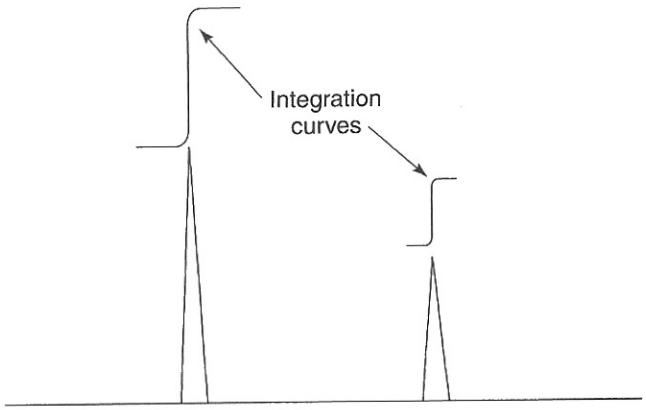


Figure 16-13: Integration curves and hydrogen peaks on an ^{1}H NMR spectrum.

For example, if there are two peaks, one with an integration curve that's 2 centimeters high and one with an integration curve that's 1 centimeter high, this tells you that the larger peak represents twice as many hydrogens as the smaller one (refer to Figure 16-14). This does not mean that the larger one represents 2 hydrogens and the smaller represents 1 hydrogen, necessarily — although this could be the case. It simply tells you that the ratio of hydrogens in the two chemical environments is 2:1. I show you how to measure an integration with a ruler in Figure 16-14.

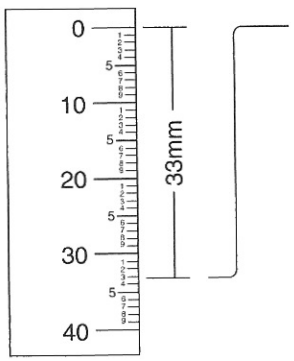


Figure 16-14: How to measure the height of integration curves.

Catching on to coupling

Ethanol, the alcohol found in beverages, is a common organic compound. The NMR spectrum for ethanol is shown in Figure 16-15.

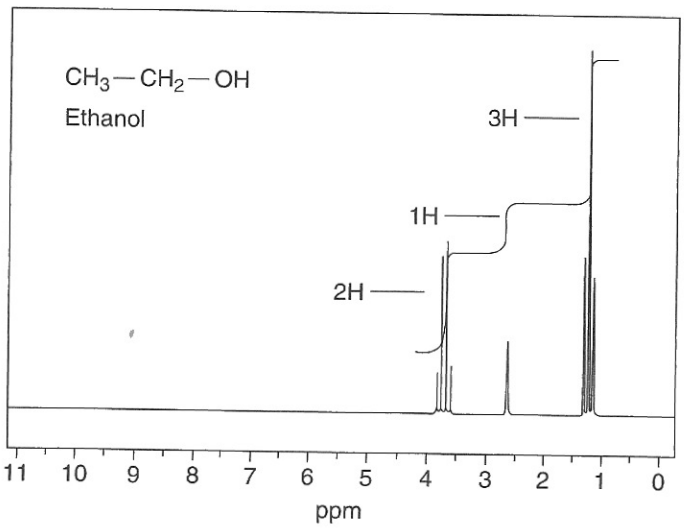


Figure 16-15: The NMR spectrum of ethanol, with the ratios of hydrogens shown beside the integration curves.

Ethanol has three kinds of hydrogens that are in unique chemical environments — the three hydrogens on the methyl group (CH_3), the two hydrogens on the methylene group (CH_2), and the hydrogen on the alcohol group (OH). That's why you see three peaks in the NMR spectrum and why the integration has a ratio of 2:1:3, representing the methylene group, the alcohol group, and the methyl group hydrogens, respectively. Notice, though, that each of the individual absorptions is split further into smaller peaks. This is called coupling. *Coupling* is a phenomenon that's useful in determining how each piece of the molecule is connected to the others. If integration tells you about the number of hydrogens a peak represents, coupling tells you how many hydrogens live next door to that hydrogen. Coupling comes from the interaction of the magnetic moments of the hydrogens with the magnetic moments of the neighboring hydrogens. In most cases, hydrogens only couple the hydrogens that are on adjacent carbons. Chemically equivalent hydrogens don't couple, which is why hydrogens on the same carbon don't couple most of the time and why the six hydrogens in benzene don't couple.

The "n + 1 rule" and the coupling constant

Coupling follows what is called the *n + 1 rule*. This rule says that a peak will be split $n + 1$ times, where n is the number of equivalent neighboring hydrogens. In the spectrum for ethanol (refer to Figure 16-12), for example, the methyl (CH_3) group has as its neighbor a carbon that has two equivalent hydrogens, so the methyl group signal is split into three peaks following the $n + 1$ rule (observed by the signal at δ1.2 ppm). The methylene group (CH_2) is next to three equivalent hydrogens on the adjacent methyl group, so its signal is split into four peaks following the $n + 1$ rule (see Figure 16-16). The hydrogen on the alcohol group doesn't couple, for reasons I talk about in the subsequent section on proton exchange.

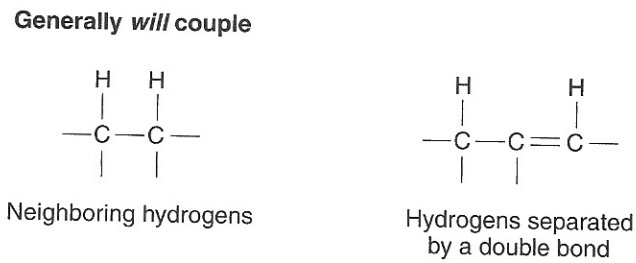


Figure 16-16: The types of hydrogens that will and won't couple.

A peak that does not couple and just shows a single line is called a *singlet.* The alcohol hydrogen in ethanol does not couple so it gives a singlet. A peak that's split into two is called a doublet, three a triplet, four a quartet, and so on. You can see the general picture for these kinds of peak splittings in Figure 16-17. The *coupling constant,* or *J value,* is the distance between the lines (or the tops of the peaks) in a signal. This value is given in frequency units (hertz, or Hz), rather than in ppm, to make the coupling constant independent of the size of the external magnetic field. The main point to remember about coupling constants is that hydrogens that couple each other have peaks that are separated by the same coupling constant. This can be a useful piece of information in determining which hydrogens are next to one another, especially when the number of peaks alone is insufficient. Returning to the ethanol example (refer to Figure 16-11), because the CH_3 and the CH_2 units couple one another, the three peaks around 1.2 ppm are the same distance apart as are the four peaks around 3.7 ppm, and both sets of peaks have the same coupling constant.

Determining coupling between non-equivalent hydrogens

Many organic molecules — particularly larger molecules — contain hydrogens that are adjacent to two or more nonequivalent hydrogens. In this scenario, adding up all the hydrogen neighbors and applying the $n + 1$ rule won't work. Instead, you need to apply the $n + 1$ rule to each nonequivalent set of hydrogens separately.

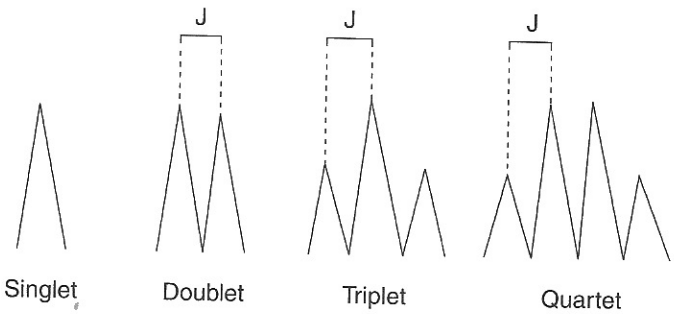


Figure 16-17: The coupling constant, or J value, for various peaks.

Take the case shown in Figure 16-18. To determine the number of peaks that you'll see for the boxed-in hydrogen — which is surrounded by two nonequivalent sets of hydrogens — you must apply the $n + 1$ rule to each of the nonequivalent hydrogens separately. For the CH_2 unit on the right, the $n + 1$ rule tells you that this will split the signal into three peaks; for the lone hydrogen on the left, the $n + 1$ rule tells you that this hydrogen will split the signal into two peaks. To get the total number of peaks you could see, you multiply the two results together. Multiplying three by two gives a total of six peaks for the boxed-in hydrogen signal.

In practice, though, you often don't see all of the possible peaks on a spectrum for a hydrogen that's surrounded by nonequivalent hydrogens, because the coupling constants for the nonequivalent hydrogens often have nearly the same value. When the coupling constants have nearly the same value, the signals overlap, and you observe fewer peaks than the maximum number possible.

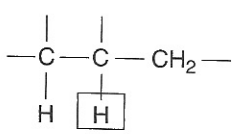


Figure 16-18: A hydrogen (proton) surrounded by nonequivalent hydrogens (protons).



In practice, you can often approximate the number of expected signals for a hydrogen (proton) surrounded by nonequivalent hydrogens. To do this, pretend that the nonequivalent hydrogens *are* chemically equivalent. Pretend that the CH_2 and the lone hydrogen are chemically equivalent. This gives a grand total of three hydrogens, so the $n + 1$ rule would suggest that if the

coupling constant were the same (or nearly the same) the signal would be split into approximately four peaks. Although in theory you could observe up to six peaks for this hydrogen, there's a fair chance you'll observe only four.

Timber! Drawing tree splitting diagrams

Given the coupling constants of neighboring hydrogens, you can predict the splitting pattern of a hydrogen using what is referred to as a tree diagram. Suppose, for example, you were asked to predict the splitting pattern for the hydrogen H_a in Figure 16-19, and you were given the coupling constant between H_a and H_b (J_{ab}) and the coupling constant between H_a and H_c (J_{ac}).

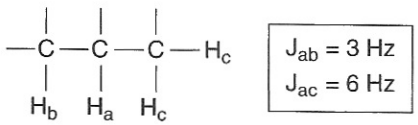


Figure 16-19: Predicting coupling patterns.

To draw the tree diagram, start with one of the neighboring hydrogens and determine how many times that hydrogen will split the signal. You'll get the same result no matter which neighboring hydrogen you start with (in this case, whether you start with H_b or H_c), but it's often easier to start with the hydrogen that gives the larger J value. So, in this case, start with the H_c protons, because the coupling constant between H_a and H_c is larger than the coupling constant between H_a and H_b. Because there are two H_c hydrogens, these hydrogens split the H_a signal into three peaks following the $n + 1$ rule.

After you determine that the H_c hydrogens will split the signal into three peaks, begin the tree diagram by making three lines, one that goes straight down, one that goes to the right, and one that goes to the left. Take a look at Figure 16-20 to see how this works. The distance between the peaks is 6 Hz, so in making your tree diagram you may want to use a ruler to measure 6 cm, 6 mm, or 6 pinky-tip lengths to represent the separation between the lines to a proportionally correct distance.



Instead of measuring the distance on your tree diagram, you could instead draw your tree on graph paper, using one or more squares of the graph paper to represent 1 Hz.

After diagramming the J value for H_a and H_c, do the same for H_a and H_b. Because there is only one H_b hydrogen, the signal will be split further into two, following the $n + 1$ rule. So, in your drawing, split each of the three lines into two additional lines, keeping a separation of 3 Hz (which would be 3 cm, 3 mm, or 3 pinky-tip lengths across) between the lines. Where each line ends, a peak would be found on the spectrum. In this case, you would expect the signal for that hydrogen to be split into six peaks in the ^{1}H NMR spectrum.

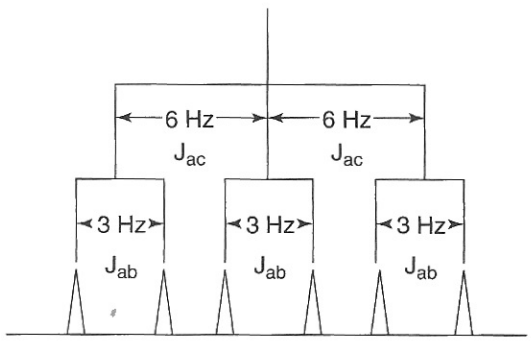


Figure 16-20: The tree diagram for the molecule in Figure 16-15, showing the origin of the six peaks for H_a.

Swapping protons: Exchange

Hydrogens attached to either oxygen or nitrogen generally don't show any kind of coupling. These peaks are found in ^{1}H NMR spectra as fat singlets. This lack of coupling is caused by chemical exchange.

Small impurities of base or acid in a sample (which are often very difficult to remove) can catalyze the exchange of the hydrogens attached to either nitrogens or oxygens — in other words, the hydrogens of alcohols or amines (see Chapter 5 for more about these functional groups). In solution containing a trace of base, for example, the hydrogens attached to nitrogens and oxygens are deprotonated by the base and then reprotonated very rapidly. Because the NMR experiment takes a long time compared to the quickness of the proton exchange, coupling is not observed for these protons except in meticulously purified samples, or at very low temperatures where this chemical exchange is slower.



Because this exchange is so quick, to determine whether a peak is an alcohol or an amine, chemists often add a drop of D_2O (or heavy water) to the sample. Because *deuterons* (deuterium nuclei) are not observed in a proton NMR, when the *deuterium* (hydrogen atom with an additional neutron) replaces a hydrogen through this process of exchange, the peak shrinks or disappears entirely. This confirms that the peak was either an alcohol or an amine.

Considering Carbon NMR

^{13}C NMR is in many ways similar to ^{1}H NMR, only simpler (yay!). Carbon NMR, though, is less sensitive than proton NMR, because only ^{13}C nuclei are NMR active; ^{12}C nuclei are inactive. Because the ^{13}C isotope only has a natural

abundance of 1.1 percent (^{12}C makes up most of the rest of the natural abundance), and because the carbon nucleus is less sensitive than a hydrogen nucleus, you generally need more sample for ^{13}C NMR than you do for ^{1}H NMR. For these two reasons, carbon NMR experiments also take quite a bit longer (hours or days rather than minutes).

Generally, you won't see either integration or coupling on a ^{13}C spectrum (although occasionally they do pop up). You don't see carbon-carbon coupling because the natural abundance of ^{13}C is so low — the chance that two ^{13}C nuclei will neighbor each other is so small as to be insignificant. You could see ^{13}C-^{1}H coupling, but most NMR experiments decouple these interactions (doing this increases the intensity of ^{13}C signals, for somewhat complicated reasons). Because of this decoupling, ^{13}C NMR peaks are often just singlets, as can be seen in the ^{13}C spectrum for butyric acid (Figure 16-21).

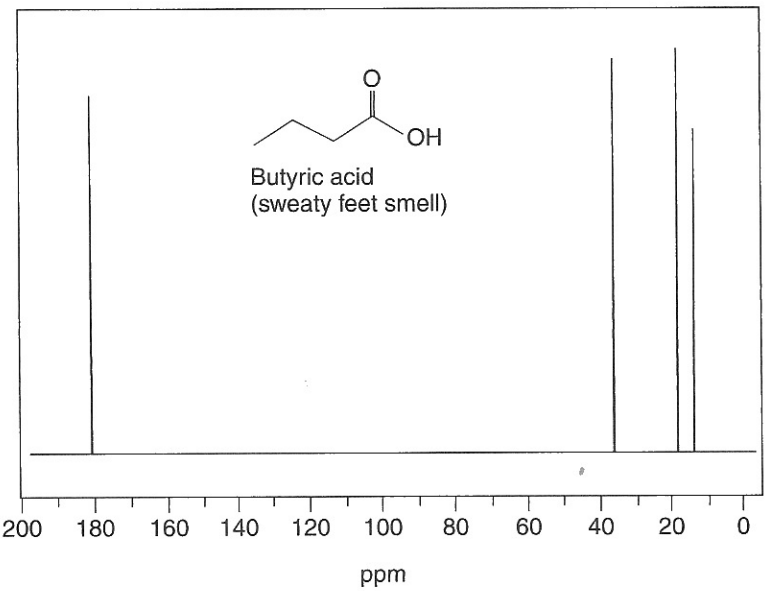


Figure 16-21: The ^{13}C spectrum of butyric acid.

Therefore, ^{13}C NMR is mostly useful for telling you the number of different kinds of carbons in a molecule from the number of peaks in the spectrum, while the chemical shift gives you an idea of the chemical environment of those carbons. The range of chemical shift values in a carbon spectrum is quite a bit broader than the shift in a proton NMR — the range is from 0–200 ppm, with a 200 ppm peak representing a highly deshielded nucleus. Keep in mind that hydrogen peaks don't show up on a ^{13}C NMR, just as ^{13}C peaks don't show up on a ^{1}H NMR spectrum; the ^{13}C NMR and ^{1}H NMR spectra must be

taken separately (although you can typically use the same NMR spectrometer to take both spectra). Figure 16-22 gives some of the ranges of chemical shift values for particular carbon types.

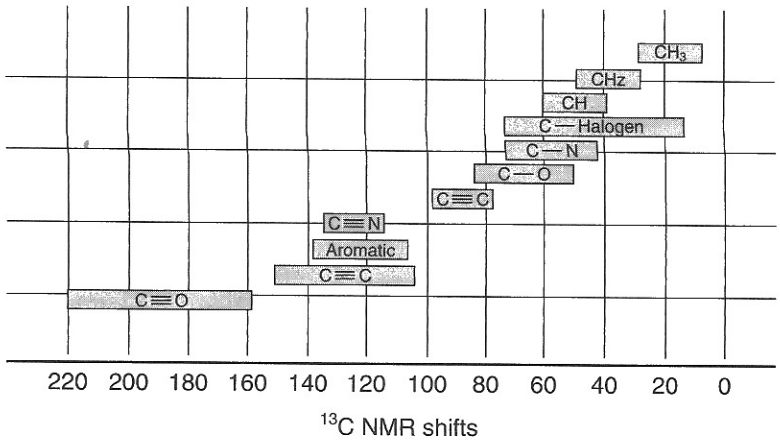


Figure 16-22: The range of values for ^{13}C NMR spectra.

Checklist: Putting the Pieces Together

Use the following definitions to help you put everything in this chapter together.

- **Chemical shift:** Refers to where a peak appears on a spectrum, relative to the reference molecule TMS (also called the δ *value*). The chemical shift is given in units of parts per million (ppm). It gives you an idea of what kinds of functional groups a hydrogen or carbon is surrounded by.
- **Integration:** Tells you the area underneath a peak, which in turn gives you information about how many hydrogens a peak represents, relative to the other peaks in the spectrum. Carbon NMR usually does not have integration on the peaks.
- **Coupling:** Tells you how many hydrogen neighbors a hydrogen sees, following the $n + 1$ rule. The $n + 1$ rule can be applied all at once if a hydrogen is surrounded only by chemically equivalent hydrogens. It must be done individually when it's surrounded by two or more chemically nonequivalent hydrogens. NMR tree-splitting diagrams are used to predict how many peaks will be found in the spectrum of a given hydrogen that's surrounded by two or more nonequivalent hydrogens. Hydrogens on either nitrogen or oxygen generally don't couple because of fast exchange processes — these hydrogens generally show up as fat singlets (which go away when the sample is shaken with D_2O).

- **Coupling constant:** Tells you the distance between the tops of the peaks in a multiplet. The coupling constant is referred to as the J value (given in units of Hz). This value can tell you which hydrogens are coupled to each other because coupled hydrogens have the same coupling constant.

Turning NMR to MRI

NMR has been widely used not only in chemistry, but also in medicine. To take a snapshot of your insides, doctors often perform x-rays. But x-rays have their limitations, particularly in looking at soft tissue. A more powerful technique is what is called MRI, which stands for Magnetic Resonance Imaging. MRI machines are just huge, specially designed NMR spectrometers that can map what your insides look like in three dimensions and can detect any abnormalities such as tumor growth or bone injury. Instead of sticking a small tube into the spectrometer as you would in a typical NMR spectrometer, in an MRI machine *you* are the sample, and you're are strapped into a very large donut-shaped magnet where a reading can be taken.

The name was changed from NMR to MRI because patients balked when they heard the name Nuclear Magnetic Resonance — nobody wanted to get in a machine that was nuclear! Of course, they didn't know that nuclear referred to the *nucleus* of the atom, not to a nuclear reaction. Still, the name was changed to Magnetic Resonance Imaging to make people feel more comfortable about the procedure. These MRI machines are designed to look for the quantity of hydrogen atoms in a given section of the body. Because different kinds of tissue have different numbers of hydrogen atoms than other kinds of tissue (normal brain tissue will have a different quantity of hydrogen than tumor tissue, for example), doctors can map out the densities using a computer and then try to detect any abnormalities. MRI is so valued in modern medicine that in 2003 the Nobel Prize in Medicine went to Paul Lauterbur and Peter Mansfield for the development of this technique.

Chapter 17

Following the Clues: Solving Problems in NMR

In This Chapter

- Tackling NMR problems
- Using clues to determine structure
- Avoiding common NMR problem-solving mistakes

I realize that spectroscopy problems are intimidating, particularly when you're first approaching them. A spectrum presents so much information, so many peaks and lines and squiggles that trying to interpret one for the first time can make you feel like a child trying to read *Moby Dick*. The amount of information to absorb makes it hard to even know where to begin.

The trick is not to get intimidated or discouraged. You may groan when you hear this now, but after you've worked enough problems to become good at them, solving spectroscopy problems can be really fun. Think of these problems as puzzles whose rules happen to be dictated by nature.

In this chapter, I present a general guide to figuring out the structures of molecules using NMR (for a description of how NMR works, see Chapter 16). Unfortunately, what I present isn't a definitive guide, because chemists don't have an indisputable "right way" to solve every NMR problem. Because of this, many textbooks don't give a specific problem-solving strategy. Instead, they instruct you to "work lots of problems" and assure you that after a while and lots of hard work you'll get the hang of it. Working many problems is indeed excellent advice, but leaves you in the awkward position of not knowing where to begin. As a result, students often start in the wrong places (I talk about common mistakes a little later in this chapter), and they often never grasp how to work these types of problems. Come exam time, they're often ready to admit themselves to the local psychiatric ward.

Because of the difficulty so many students have with solving problems in NMR spectroscopy, I present the structure-solving strategy that works for me and that's worked for others. I suggest that it might work for you too, at least as a foundation until you're confident enough to alter it to fit your own learning style and adapt it to the particular problem at hand. Spectroscopy problems can be particularly intimidating because they can be solved in a number of different ways. But the way I like to determine the structure of a compound using NMR is systematically, by following the clues.

Follow the Clues

I like to think of solving spectroscopy problems as analogous to a detective in the dark with a flashlight, searching for "whodunit." Methodical clue gathering is the best way to determine the culprit — the mischievous compound in this case — rather than blindly waving the flashlight (or pencil) about, hoping for some sort of chance epiphany (which never comes during an exam, but only after you turn it in).

You're likely to encounter many different kinds of NMR problems. Many problems will give you at least the molecular formula and the ^{1}H NMR. Some problems will also provide the IR spectrum, mass spectrum, and ^{13}C NMR spectrum as well. This clue-gathering technique I give you can be tailored to fit just about any of these problem types; simply ignore any clues that don't apply to the particular problem that you're working on. After I tell you about how to gather all of the clues, I use two examples to show you how to apply this guide to real problems.

Here's the rundown of how the clue gathering works. You start by determining the degrees of unsaturation from the molecular formula. This gives a quick indication of whether the compound contains rings, double bonds, or triple bonds, or whether the molecule is saturated. A more definitive indication of what kind of molecule you're dealing with can be found by looking at the IR spectrum (if you're given one in the problem) and also by a quick peek at the ^{1}H NMR for peaks that scream out a particular functional group (specifically, carboxylic acids, aldehydes, and aromatic rings). Next, you use the integration (plus the clues from the degrees of unsaturation and the IR) to determine all of the fragments of the molecule. With fragments in hand, you put the pieces together in a way that's consistent with the chemical shift and the peak splitting. Finally, you double-check your proposed structure by making sure that everything is consistent with all of the clues. In short, you first determine all the pieces of the molecule, and then you try to fit them together in the correct way.

That's the big picture of how you solve a structure with this technique. Next, I cover the practical details of each of those steps. So switch on your flashlight, detective — here's how to gather those clues!

Clue 1: Determine the degrees of unsaturation (DOU) from the molecular formula



For a reminder on degrees of unsaturation, mosey on over to Chapter 8.

If you're given the molecular formula, just plug the formula into the equation:

$$\text{degrees of unsaturation} = \frac{\left[(\text{number of carbons} \times 2) + 2\right] - \text{number of hydrogens}}{2}$$

If you have a formula with more than just carbons and hydrogens, you also need the following conversions:

- **Halogens (F, Cl, Br, I):** Add one hydrogen to the molecular formula for each halogen present
- **Nitrogen:** Subtract one hydrogen for each nitrogen present
- **Oxygen or sulfur:** Ignore

The degree of unsaturation (DOU) is a valuable clue because it tells you how many double bonds, triple bonds, or rings must be present in the unknown compound (although it doesn't tell you *which* of these elements of unsaturation are present).



Double bonds and rings count for one degree of unsaturation each, and triple bonds count for two degrees each. If the molecule has zero degrees of unsaturation, you know that there are no double bonds, triple bonds, or rings in the molecule.

Clue 2: Look at the IR spectrum to determine the major functional groups present in the unknown compound

To brush up on IR spectroscopy, see Chapter 15. If possible, confirm the presence of the major functional groups in the NMR spectrum. Easy ones to confirm include aldehydes, carboxylic acids, and benzene rings.

Clue 3: Determine the peak ratios by measuring the heights of the integration curves

Determine how many hydrogens each peak represents by comparing the ratios to the molecular formula. Especially if you're just starting to learn how to solve ^{1}H NMR problems, using a ruler can be indispensable for finding out the relative integration ratios. What you need to measure with the ruler is the *height* of the integration curve over a given peak (the integration curve is the squiggle over a peak that looks like a capital *S*). These heights are related to the areas underneath a peak, which in turn are related to the number of hydrogens that particular peak represents. And that's what you want to figure out for this clue. Determining how many hydrogens each peak represents will help you to find the fragments of the molecule in Clue 4.

Here's an example of how to determine the integration using a ruler (see Figure 17-1; for clarity, the peaks underneath the integrations aren't shown). First, you want to establish the relative ratio between the integrations. To do this, use a ruler to measure the difference between the top and the bottom of each of the integration curves. After you measure the height of each peak on the spectrum, divide each of the heights by the smallest height. This will give you the ratios.

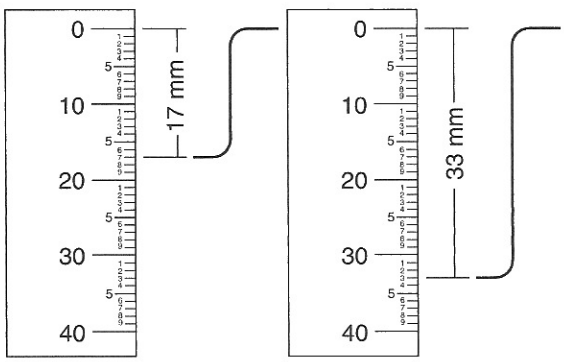


Figure 17-1: Using a ruler to measure integration peaks.

In this example, the smallest height is 17 mm, so you divide both heights by 17 mm. In this case, this gives an integration ratio of 1:1.94. Because you can never have a fraction of a hydrogen atom, you need to convert the relative ratios into whole numbers.

As is the case in this example, you will often find that the integrations don't work out to be perfect whole numbers. If the numbers are very close to whole numbers, the integrations are probably just in error by a bit, and you simply need to round them to the nearest whole number. Because 1.94 is very close to 2.0, in this case you would say that the integration is 1:2.



These imperfect integrations can be attributed to noise in the baseline, a poorly calibrated integral, impurities in the sample, and errors made while measuring the heights of the curves with the ruler.

For ratios that are not close to whole numbers, you need to multiply the ratio by the *smallest number that makes both numbers* in the ratios whole numbers. If the ratio were 1.0:1.5, for example, you would multiply both parts of the ratio by two to give a whole-number ratio of 2:3. If the ratio were 1.0:1.33, you would multiply both by three to give a whole-number ratio of 3:4, and so on.

So, for this example, you could say that your relative ratio of hydrogens is 1:2. Alternatively, using organic-speak, you could say that the peak on the left integrates for one and that the peak on the right integrates for two.

But does this then mean that the peak on the left represents one hydrogen, and the peak on the right represents two hydrogens? Not necessarily. Remember that this is the relative ratio of hydrogens, not the absolute ratio, which means that you only know that the larger peak has twice the number of hydrogens as the smaller peak; you don't know the actual number of hydrogens. To find the absolute number of hydrogens you must compare your ratio to the molecular formula.

If the sum of all the numbers in the relative ratio matches the number of hydrogens in the molecular formula — in this example if there were only three hydrogens in the molecular formula — *then* you could say that the peak on the left represents one hydrogen and the peak on the right represents two hydrogens, because then all of the hydrogens in the molecule would be accounted for. But if the molecular formula had six hydrogens in it, you would have to multiply the relative ratio by two to make the number in your spectrum match the number in your molecular formula — so in that case the peak that integrates for one would represent two hydrogens and the peak that integrates for two would represent four hydrogens. If there were nine hydrogens, you would multiply the relative integrations by three, and so forth.



Remember that the sum of all the hydrogens (absolute number) that you derived from the integrations must exactly match the number of hydrogens in the molecular formula. If they don't, then you need to reconsider the values of the integrals.

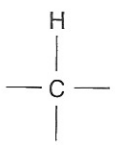
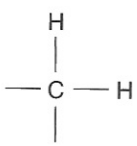
Here's a summary of the steps to determine the number of hydrogens represented by each peak:

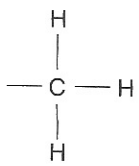
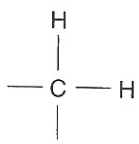
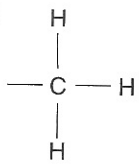
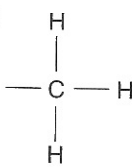
- Measure the heights of each peak using a ruler.
- Divide each of the heights by the smallest height measured.
- If one or more of the numbers are not whole numbers, convert them to whole numbers by rounding (if they are all very near a whole number) or by multiplying all of the numbers in the ratio by a whole number. This gives you the relative ratio of hydrogens in the peaks.
- To determine the actual number of hydrogens each peak represents, add each of the numbers in your relative ratio and compare this number to the number of hydrogens in the molecular formula. If these numbers are not equal, determine what you need to multiply your relative ratio by in order to make the number of hydrogens in your spectrum match the number of hydrogens in the molecular formula. If they are the same, you don't need to multiply the ratio by anything.

Clue 4: Break the NMR peaks into fragments using the integration from Clue 3

After you've determined the number of hydrogen atoms that each peak represents, you can assign each peak to a fragment of the molecule. Table 17-1 shows some common fragments.

Table 17-1 Common Fragments

Number of Hs	*Likely Fragment*	*Notes*
1H		Check the IR spectrum to make sure this is not an alcohol (OH), secondary amine (NH), aldehyde (CHO), or acid proton (COOH).
2H		Rarely: This is two symmetric CH groups.

Number of Hs	*Likely Fragment*	*Notes*
3H		Rarely: This is three symmetric CH groups.
4H	2 	Usually two symmetric methylene (CH_2) groups.
6H	2 	Rarely: This is three symmetric CH_2 groups. Often indicates an isopropyl group.
9H	3 	Often indicative of a tertiary butyl group.

As you determine the fragments in the molecule, write them all down on a sheet of scratch paper so they will be in front of you when you're ready to solve the structure. For example, if you have three peaks — one that integrates for 1H, one that integrates for 2H, and one that integrates for 3H, you would write on your scrap paper CH, CH_2, and CH_3. After you determine all of the fragments (including fragments you determined from the IR, if you're given one), add up all of the atoms in your fragments to make sure that they match the molecular formula and to be certain that you're not missing any atoms.

Clue 5: Combine the fragments in a way that fits with the NMR peak splitting, the chemical shift, and the degrees of unsaturation

Often when you're starting, the best way to go from fragments to a possible structure is to simply brainstorm all of the possible molecules that could

include the fragments you listed, because in many cases there will be more than one way to put all of the fragments together. After you've brainstormed all of the possible structures, then you systematically eliminate all of the incorrect structures. You can eliminate the incorrect structures based on a few different factors. Most often, the incorrect structures will not produce the peak splitting that you see in your NMR spectrum, or will have symmetry when your NMR spectrum suggests that the molecule is not symmetrical. But sometimes you may need to use the chemical shift to eliminate incorrect structures. This procedure may seem tedious, but after working a few problems, you will develop an intuition about which structures are likely correct, and putting together the fragments to make the correct structure will take no time at all.



After working several problems, you'll notice some common patterns. A quartet that integrates for 2H and a triplet that integrates for 3H on a spectrum is often indicative of an ethyl group ($-CH_2CH_3$). Likewise, a multiplet that integrates for 1H and a doublet that integrates for 6H usually suggest an isopropyl group ($-CH(CH_3)_2$).

Clue 6: Recheck your structure with the NMR and the IR to make sure it's an exact match

For this clue, look only at your proposed compound, then predict what the spectra should look like, going carbon atom by carbon atom. Then compare this expected spectrum of the compound you proposed to the real spectra to see if they match. Here is where you check to see if the chemical shift for each proton (H) makes sense. Remember, protons near electronegative atoms (like N, O, Br, F, Cl, and so on) will have a higher chemical shift than protons that that are not near electronegative atoms.

So what if you get to Clue 5 or Clue 6 and realize, "Oh no! My structure's wrong!"

In that case, there are two checks to spot the problem.

Check 1

The first thing to check is whether you combined the fragments in the correct way. Often, there is more than one way to put the structure together from the fragments. If you have tried all of the ways and none of them check out, then the problem is probably with the fragments themselves (see Check 2).

Check 2

A less likely possibility is that the fragments themselves are incorrect. The likely fragment in Table 17-1 will be correct in most cases — so it's certainly a good place to begin. Unfortunately, this procedure is not 100-percent foolproof. When it does fail, it's usually with molecules that have a high degree of symmetry. If the procedure fails, you will reach Clue 5 and be unable to figure out how to reasonably put the fragments back together again in a way that makes sense with the splitting and chemical shift. In that case, return to the table and rethink your choices of fragments, looking in the notes column to see alternative possibilities.

An example illustrating how the most likely fragment in the table would be incorrect is shown in Figure 17-2. Because of the symmetry in the molecule — that is, the left-hand side of the molecule is identical to the right-hand side of the molecule — the two CH_3 groups are identical and will show a single peak (with an integration of 6H), and the two CHs will also show a single peak (with an integration of 2H).

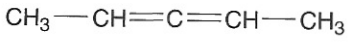


Figure 17-2: Dimethyl allene.

From the 6H row of Table 17-1, the two symmetrical CH_3 fragments are predicted correctly in the "Likely Fragment" column; the 2H integration, however, is predicted to be a CH_2 fragment rather than two identical CH fragments. Here, choosing the likely fragment (and not the rare case) from the table, you would reach Clue 5 and be unable to piece together a sensible structure. Going back to the "Notes" column in Table 17-1 and looking at the integration for 2H, you see that in rare cases this integration could also represent two symmetrical CH fragments. Making this substitution, then, would lead you down the road to the correct answer.

Working Problems

Here's an example of a bare-bones problem — one where you're given just the molecular formula and the ^{1}H NMR and asked to solve the structure. When you're doing problems on your own, write all the clues you find on a sheet of scratch paper, just as a detective would write down all of the clues in a notepad, so that they'll all be in front of you when you're ready to solve the murder, er the structure.

Example 1: Using the molecular formula and NMR to deduce the structure of a molecule

Determine the structure of a compound whose molecular formula is $C_8H_8O_2$, using its ^1H NMR spectrum in Figure 17-3.

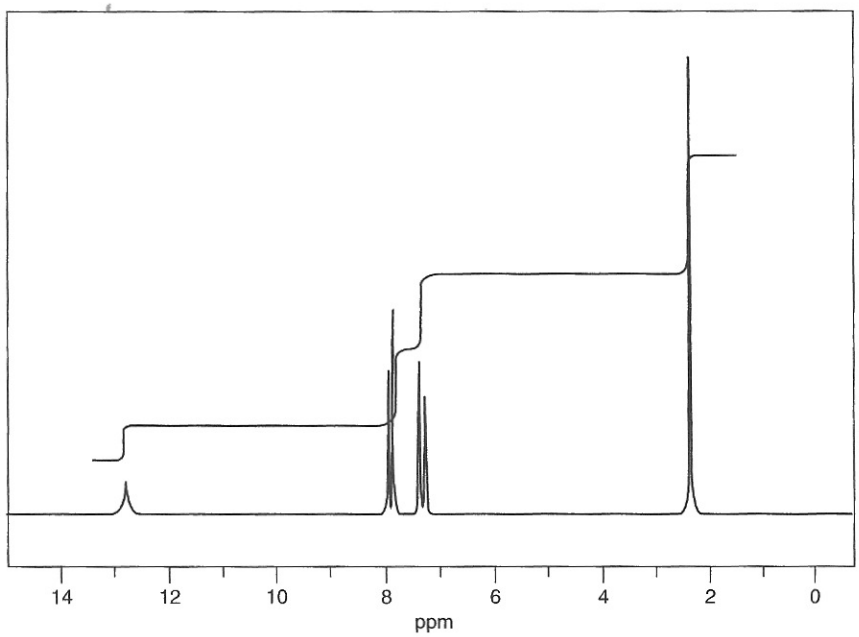


Figure 17-3: The NMR spectrum for a compound with molecular formula $C_8H_8O_2$.

The way to tackle a problem like this is to work through it systematically, clue by clue.

Clue 1: Determine the degrees of unsaturation

Plugging the molecular formula, $C_8H_8O_2$, into the equation gives you five degrees of unsaturation.



Whenever you see four or more degrees of unsaturation in a molecule, the molecule likely contains a benzene ring. To confirm this, look for peaks around δ6.5–8.5 ppm in the ^1H NMR. Benzene rings account for four degrees of unsaturation (three for the three double bonds and one for the ring).

Clue 2: Determine the major functional groups

In this problem, you're not given an IR spectrum to determine the functional groups. However, you can still look at the NMR to see if any peaks indicative of functional groups are present. The three biggies to look for in the ^{1}H NMR are:

- Carboxylic acid protons around δ12 ppm (short, fat peaks)
- Aldehyde protons around δ10 ppm
- Aromatic protons between δ6.5 ppm and δ8.5 ppm

Only rarely (rarely, that is, in problems seen in an undergraduate class) do any other types of protons absorb in these regions.

In the example in Figure 17-3, you have both a carboxylic acid (the short fat peak around δ13 ppm), and a benzene ring (the two sets of peaks between δ7 ppm and δ8 ppm), which you would have suspected earlier from the number of degrees of unsaturation. (For a list of chemical shifts in NMR produced by common functional groups, see Chapter 16.) Write down those two portions of the molecule on your scratch paper as shown in Figure 17-4.

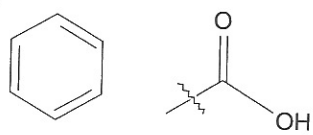


Figure 17-4: Carboxylic acid and a benzene ring.



After you've identified from the NMR spectrum the peaks that belong to particular functional group, put a check next to these peaks on the spectrum so that you don't reassign them to fragments in Clue 4. In this example, you would put a check next to the benzene protons and the carboxylic acid proton, as they've already been assigned to fragments.

Clue 3: Determine the peak ratios

For this step, you first want to figure out the height ratios for the four peaks on the spectrum. Going from left to right across the spectrum, the ratio is 1:2:2:3. If you can't see that by just looking at the spectrum, break out a ruler and physically measure the size of the integration lines just as I did in the preceding example and prove to yourself that this ratio is correct.

Now that you have the relative ratio (1:2:2:3), you need to convert that ratio into the absolute number of hydrogens that each peak represents. In this case, the molecular formula ($C_8H_8O_2$) tells you that 8 hydrogens are in the molecule.

Because the relative ratio adds up to 8 (1+2+2+3), you don't have to multiply the ratio by anything; the relative ratio is also the absolute ratio. You now know that the first peak represents 1H, the second and third peaks represent 2H, and the fourth peak represents 3H.

Clue 4: Finding the fragments

You've already determined from Clue 2 that the peak at around δ12 ppm is from a carboxylic acid proton, and that the two peaks between δ7 ppm and δ8 ppm are from a benzene ring. So you've accounted for all of the peaks in the NMR except for the peak at δ2.3 ppm that integrates for 3H. From Table 17-1, you find that 3H represents a $-CH_3$ fragment. Jot that down on your scratch paper.

Now, take a closer look at the peaks for the benzene ring. From the integration, you know that the benzene has four hydrogens. This tells you that the ring must be substituted exactly twice; that is, that two non-hydrogen groups are attached to it.



If the aromatic region has five protons, then you have a benzene ring that's substituted once. If it has four protons, it's substituted twice (disubstituted). If it has three protons, then it's substituted three times (trisubstituted). If you need to, draw the structures out to prove this to yourself.

If you have a disubstituted benzene, as in this case, you must determine the orientation of the substituents relative to each other. A disubstituted benzene ring can have three different orientations. The substituents can either be ortho, meta, or para to each other (see Figure 17-5; for a review of aromatic substitution patterns see Chapter 13).

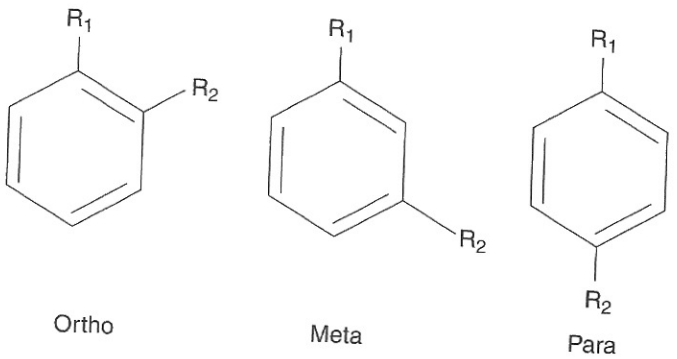


Figure 17-5: The three possible orientations for a disubstituted benzene ring.

Because benzene contains four hydrogens, you might expect to see four peaks, one for each hydrogen. However, in the spectrum you can see only two peaks in the aromatic region. This suggests a plane of symmetry in the molecule. Looking back at Figure 17-4, only a para-substituted benzene has such a plane of symmetry — in this case, the left side of the ring is identical to the right side.

Because of this symmetry (see Figure 17-6), the two hydrogens neighboring R_1 (labeled H_a) are in identical chemical environments (both are one carbon away from R_1 and two carbons from R_2), and the two hydrogens neighboring R_2 (labeled H_b) are in identical chemical environments. Because of this symmetry, you would expect to see only two peaks in the ^1H NMR that integrate for 2H each. This pattern is typical for para-substituted benzene rings.

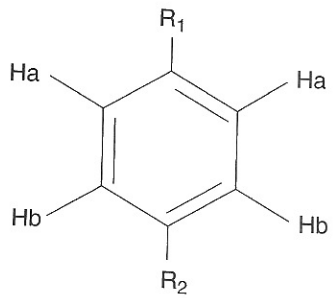


Figure 17-6: Seeing symmetry.



If you can't see the identical chemical environments from looking at the drawing, you might try building the molecule using a model so that you can turn the model over in your hands and prove to yourself that the two H_a atoms are identical, and the two H_a atoms are identical.

Now that you know that the benzene ring has two substituents that are para to each other, you can write out all of the fragments (after double-checking that the number of atoms in our fragments exactly matches the number in the molecular formula). See Figure 17-7.

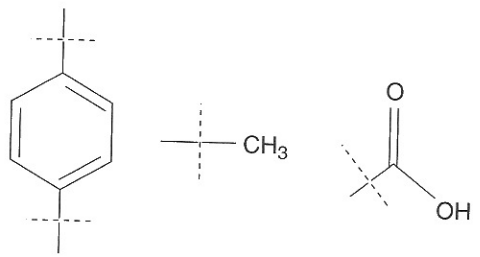


Figure 17-7: Structure fragments.

Clue 5: All the king's horses: Putting the pieces together again

In this case, there's only one possible way to put the fragments together. The proposed structure is p-toluic acid, shown in Figure 17-8.

Clue 6: Confirm the proposed structure

Double-checking to make sure that your proposed structure is the correct one is always a good idea. You check the structure by predicting what the

NMR should look like, and then comparing it to the actual spectra to make sure that it matches. So check this structure (see Figure 17-9):

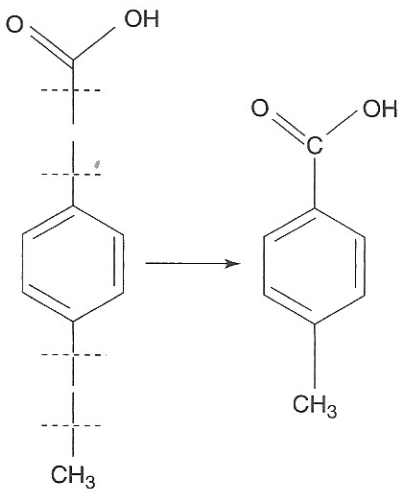


Figure 17-8: p-toluic acid.

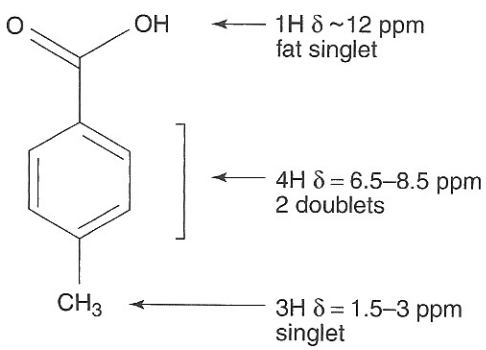


Figure 17-9: Checking the proposed structure.

- The methyl group should correspond to a peak that integrates for 3H and is a singlet. It would be at a slightly higher chemical shift because it's near an aromatic ring. At δ2.3 ppm there's a singlet that integrates for 3H. Check!
- The aromatic ring protons should show two doublets that have a combined integration of 4H between δ6.5 and δ8.5 ppm. Check!
- The carboxylic acid should have a peak at around δ12 ppm that integrates for 1H and is a singlet. Check!

Looks like you can lock this one up!

Example 2: Using the molecular formula, IR, and NMR to deduce the structure of a molecule

Solve the structure of compound $C_5H_{10}O$ that has the ^1H NMR and IR spectra shown in Figure 17-10.

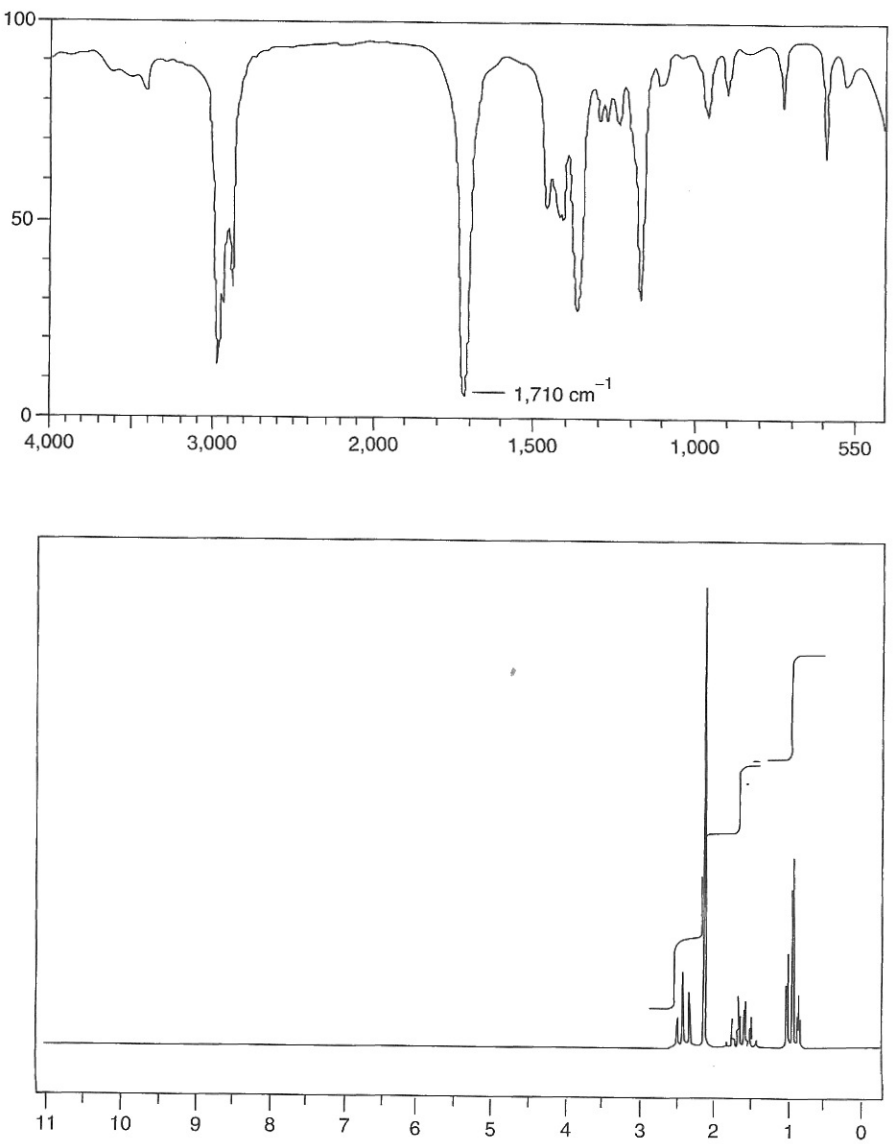


Figure 17-10: The IR and NMR spectra for a compound with molecular formula $C_5H_{10}O$.

Clue 1: Determine the degrees of unsaturation

Plugging the molecular formula, $C_5H_{10}O$, into the DOU equation, shows that this molecule has one degree of unsaturation. This indicates that the molecule has either one double bond or one ring.

Clue 2: Determine the major functional groups

The IR spectrum shows an intense peak at 1,710 cm^{-1}, which is characteristic of a carbonyl group. (See Chapter 5 for a listing of the functional groups containing a carbonyl group.) The small peaks between 3,400 and 3,700 cm^{-1} cannot be amine stretches because, according to the molecular formula, the compound doesn't contain nitrogen, and the peak is not broad and intense enough to be caused by an alcohol (besides, the oxygen is already accounted for with the carbonyl group). This is probably just a carbonyl overtone stretch. No other peaks in the IR are very helpful. (For a list of IR peaks produced by common functional groups, see Chapter 15.) Looking in the ^1H NMR for distinct peaks above δ6.5 ppm turns up nothing; the NMR spectrum shows no peaks attributable to aldehyde, aromatic, or acid functional groups. (For a list of chemical shifts in NMR produced by common functional groups, see Chapter 16.)

Clue 3: Determine the peak ratios

The NMR peaks integrate with a relative ratio of 1.0:1.5:1.0:1.5 from left to right (use a ruler if you don't believe me). Multiplying this entire ratio by two gives a whole number relative ratio of 2:3:2:3. Adding up 2+3+2+3 gives 8, matching the number of hydrogens in the molecular formula. So you don't need to multiply the relative ratio by anything to get the actual number of hydrogens. Therefore, the integrations for the three peaks from left to right are 2H, 3H, 2H, and 3H.

Clue 4: Finding the fragments

From Table 17-1, the most likely fragments for 2H, 3H, 2H, and 3H are CH_2, CH_3, CH_2, and CH_3, respectively. Adding up all the atoms from these fragments to see if the number of atoms matches the molecular formula shows that one carbon and one oxygen atom are missing. Additionally, from Clue 1 you know that this molecule has one degree of unsaturation; this unsaturation could be accounted for by the double bond in the carbonyl seen in the IR spectrum (refer to Clue 2). Carbonyl groups are found in aldehydes, ketones, esters, and carboxylic acids. Here, however, esters and carboxylic acids can be eliminated because the molecular formula shows only a single oxygen. Because the NMR spectrum doesn't contain an aldehyde peak (aldehyde protons are seen around δ10 ppm) and the IR spectrum doesn't show an aldehyde C-H stretch in the at 2,700 cm^{-1} (see Chapter 15), the carbonyl group is a ketone.

Clue 5: And all the king's men: Putting the pieces together again

Because the carbonyl is a ketone, the fragments can only be pieced together in two ways, as shown in Figure 17-11. Note that one of these ways gives a symmetric molecule (possible compound A, where the carbonyl group is in the center of the molecule) while the other way gives a molecule that's not symmetric (possible compound B, where the carbonyl group is on one side of the molecule).

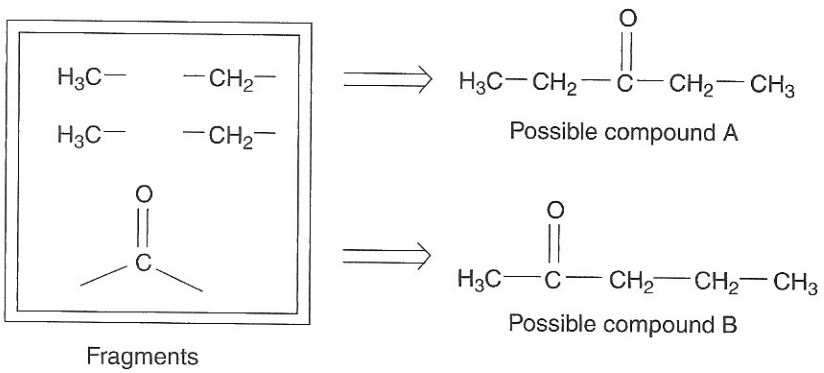


Figure 17-11: The two possible structures.

Now that you've narrowed down the choices to two, you want to check to see which one is the most consistent with the peak splitting and the chemical shift. Try possible compound A first.

You can easily rule out this compound because it has a center of symmetry — that is, the left-hand side of the molecule is identical to the right-hand side. Therefore, you would expect to see just two peaks in the ^{1}H NMR for this compound rather than the four you see, because both methyl (CH_3) groups would be in identical chemical environments, and both methylene (CH_2) groups would also be in identical chemical environments.

Clue 6: Confirm the proposed structure

So now check possible compound B (Figure 17-12).

This compound has no symmetry, so you go carbon atom by carbon atom to check the structure.

- The far left methyl group has no adjacent hydrogens. Therefore, it would be a singlet and integrate for 3H. Because it's next to the electron-withdrawing carbonyl group, you would expect it to be shifted downfield (higher ppm). Sure enough, the NMR shows a singlet at δ2.1 ppm that integrates for 3H. Check!

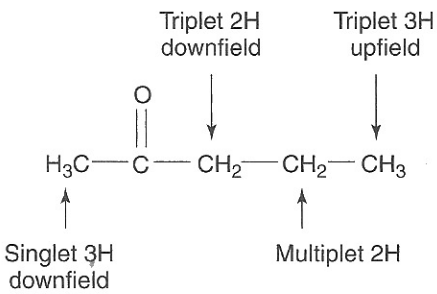


Figure 17-12: Confirming the structure.

- The methylene (CH_2) to the immediate right of the carbonyl group would be expected to be a triplet, because it's adjacent to two hydrogens. This triplet would integrate for 2H and would be expected to be at higher chemical shift because it's next to the electron-withdrawing carbonyl group. Sure enough, at δ2.5 ppm there's a triplet that integrates for 2H. Check!
- The methylene group further to the right would be expected to be a multiplet because it's adjacent to five hydrogens (it would be approximately a sextet, although it could split into as many as 12 peaks—see Chapter 16), and would integrate for 2H. Sure enough, at δ1.5 ppm the NMR spectrum shows a multiplet (that appears to be a sextet) that integrates for 2H. Check!
- The methyl to the far right would be expected to be a triplet because it's adjacent to two hydrogens and would integrate for 3H. This triplet would be expected to be farther upfield (lower ppm) than the other peaks because it's the farthest away from the electron-withdrawing carbonyl group. Sure enough, at δ0.9 ppm the NMR spectrum show a triplet that integrates for 3H. Check!

Everything matches, so you can cuff this one up.

Three Common Mistakes in NMR Problem Solving

In NMR problems, there's so much information to be considered, that making a mistake is easy. But here are three common mistakes that you can try to avoid when solving NMR spectroscopy problems.

Mistake 1: Trying to determine a structure from the chemical shift

Chemical shift regions overlap, so attempting to determine all of the fragments of a molecule solely on the basis of chemical shift is almost always a mistake. A few fragments can be determined in some cases — aldehydes, carboxylic acids, and aromatic ring fragments are often given away by the chemical shift — but most fragments cannot. A proton at δ2.5 ppm could be a proton adjacent to a carbonyl group; it could also be a proton neighboring a benzene ring or even a proton on a double bond. It would be impossible to tell the difference between these three possibilities simply by looking at the chemical shift.

Yes, there are chemical shift tables big enough to choke a small beluga whale, but your time will be much better spent understanding the general ideas behind the chemical shift than memorizing all of the values for every conceivable proton that you might encounter. Such mindless memorization is a fruitless task anyway. You might know that a proton next to a chlorine will have a chemical shift of δ3–δ4 ppm, but what about a proton next to two chlorines? Or what about a proton next to two chlorines and a carbonyl group? Too many possibilities exist to simply memorize them all.

A better approach is to learn the ranges of chemical shifts for protons next to the common functional groups (such as those found in Chapter 16; many professors are kind enough to give you a table that they want you to learn), and then understand the idea behind the chemical shift. If you understand that protons next to groups that have a local magnetic field (like double bonds, triple bonds, and aromatic rings) will have a higher chemical shift than isolated protons, and that protons next to electronegative elements will have a higher chemical shift than those that are far from electronegative elements, you will be in pretty good shape. If you understand these concepts, you won't need a table to know that a proton next to two chlorines will have a higher chemical shift than a proton next to one chlorine. This understanding will give you greater flexibility for solving NMR problems.

Mistake 2: Starting with coupling

Unless you really know what you're doing, trying to solve a structure by looking first at the coupling will result in fistfuls of your pulled-out hair and several empty bottles of aspirin. Unlike integration, coupling doesn't refer to how many hydrogens (protons) a peak represents, but indicates instead how

many proton neighbors a certain hydrogen has. Because of that fact, determining the pieces of the molecule using the coupling is much more difficult than using the integrations.

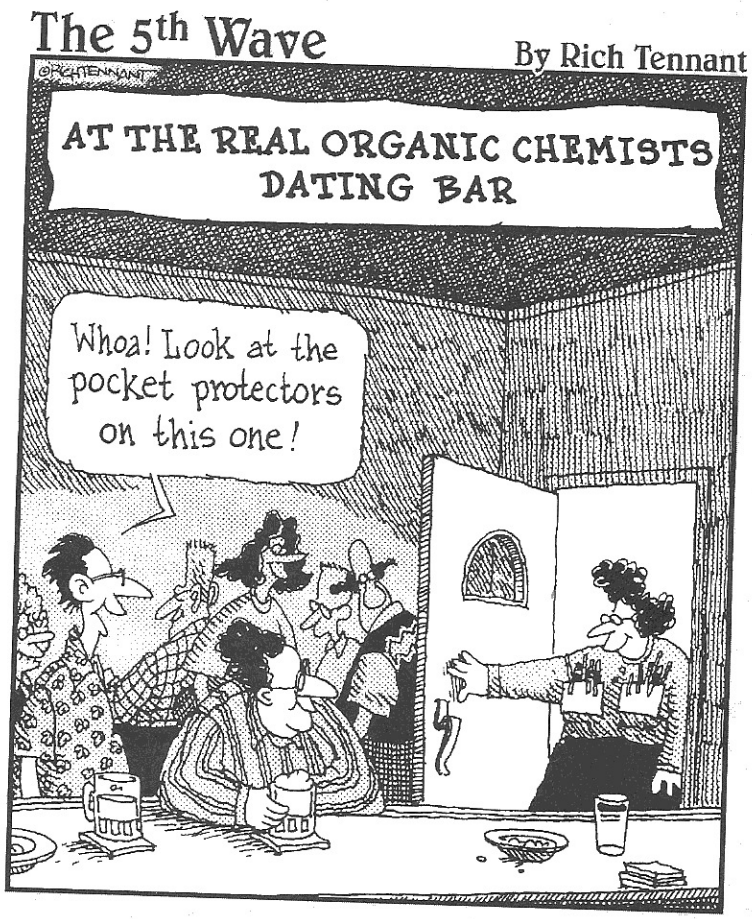
Think of this process as analogous to the work of a census taker going house to house gathering information about the number of residents in each house. If you were taking the census, what would make your job easier, having people tell you how many people lived in the house you were visiting, or having people tell you how many people lived next door to the house you were visiting? Doing the census would be easier if the residents told you how many people lived in that particular house, right? To continue with this analogy, the integration tells you how many people (hydrogens) live in the house (the specific carbon); the coupling tells you how many people (hydrogens) live next door.

Another drawback to starting with coupling is that coupling has so many nuances (many of which are beyond the scope of undergraduate-level NMR), and peaks are not always split into the standard-fare singlets, doublets, triplets, and so on. Long range coupling (which I don't cover in this book) can complicate things, as can the presence of chiral centers (refer to Chapter 6). Protons that are next to nonequivalent hydrogens can give some pretty complicated splitting patterns, too. Often you just get a haystack — a big jumble of many peaks clumped together that are hard to resolve. Sometimes the coupling will also be hard to see unless your professor was kind and magnified the peaks for you. Because of all these factors, coupling is most useful for determining the *connectivity* of the fragments, and is less useful in determining the *identity* of the fragments themselves.

Mistake 3: Confusing integration with coupling

Remember that the integration tells you the relative number of protons a peak represents, but that coupling refers to how many neighbors those protons see. Therefore, the $n + 1$ rule only applies to coupling, not to integration, and has nothing to do with how many protons a peak represents. A multiplet can integrate for 1H just as a singlet can integrate for 9H. Coupling and integration are independent of one another.

Part V
The Part of Tens



In this part . . .

In any field, there are those who made the big breakthroughs. Think Einstein and Newton for physics, and Freud and Jung for psychology. In this part, I present ten giants in organic chemistry who shook the field to its core. I also give you ten tips that help you do well in organic chemistry, and I include ten cool organic discoveries, just for fun.

Chapter 18

Ten Keys for Surviving Orgo

In This Chapter

- Discovering the secrets of o-chem success
- Making organic painless and fun
- Developing good study habits and test-taking skills

Organic chemistry has a reputation for being a challenging course. But here's the thing that's often not mentioned: Organic chemistry is a subject that anyone can ace. Doing well, though, requires working not only hard but also working efficiently. So this chapter gives you practical tips on how to study as efficiently as possible so you can do well in the class.

Have a Good Attitude

I put this first because probably the most important key to surviving organic chemistry is to have the right attitude. Even if you aren't thrilled at the idea of taking organic chemistry and don't think you'll ever use it in whatever career you're pursuing, you need to come into the class with a positive attitude. If you decide to make the best of the class and to learn as much as possible, studying will be a lot easier. With a good attitude, organic chemistry might turn out to be quite a bit of fun, and if it's fun for you, it'll be easier to force yourself to sit down and study the material. With a bad attitude, studying for the class would be harder than trying to get a 10-year-old to hold still for a booster shot.

Work the Problems

Of course, if you have a great attitude but don't take the time to work the problems, the results will still be ugly. No one— not you, not me, not Einstein (well, maybe Einstein) — can master organic chemistry without working the

problems. And not only do you have to work the problems, but you have to work the problems honestly — that is, you have to try them by yourself without sneaking a peek at the solutions guide until after you've finished the problem. It's not enough to look at the solutions guide and say to yourself, "yup, I can do that, by golly. That sure *looks* right." Because on an exam you're not going to have a little checkbox that says "Does this answer look right to you? Check yes or no." It's going to be a question with a bit of blank space staring groggily back up at you, waiting to be filled in. Most textbooks have problems worked into the text of the chapters, and these are often helpful in seeing if you've mastered the critical concepts of that section. Do these problems as you read the book.

Some people find working in groups helpful, and some studies suggest that working in groups is one of the best ways to learn. I personally have always been distrustful of group work, because a lot of organic chemistry just needs to be learned on your own, and groups often get into bad patterns (like one person doing all of the work and the rest copying, for example). A group is probably not going to help you memorize the functional groups, but it may help you to discover how to tackle problems, if everyone in the group pitches in. If you've worked in groups before and you know groups work well for you — particularly if you know the people who are going to be in the group — then that's great. Use group work to your advantage.

But regardless of how you choose to study, you can't get through organic chemistry without working the problems.

Don't Fall Behind

Organic chemistry is probably the fastest paced course that you will take while an undergraduate. Organic textbooks usually span a thousand pages or more, and a majority of that will probably be covered in a two-semester class (and it's not exactly like thumbing through a Stephen King novel). If you fall behind, it's nearly impossible to catch up. So make a schedule and do a little organic chemistry every day.

Part of not falling behind is taking advantage of your most precious resource: time. In an ideal Utopian world — which is the world that many professors seem to believe students live in — you would have enough time to be able to understand and master every single concept and idea in organic chemistry. In the real world (which is the one where students have part-time jobs, other classes, family and medical emergencies, and — get this — lives), things don't always work out that way.

Doctors in emergency rooms use a concept called the *triage principle* for allocating resources when there's not enough to go around. A person with a gunshot wound gets medical resources at the expense of the person with a headache. Time is your most precious resource. Spend it wisely using this principal of triage. For example, if you have little time left before an exam, rather than spending three hours memorizing a data table that may be represented by one problem on an exam, use the same amount of time to master an important idea in organic synthesis that will be represented on half the exam. In other words, be practical when you study.

Reviewing old exams that are on file are extremely high-yield studies, because you get an idea of what a professor thinks is important and — perhaps even more crucially — what he or she thinks is unimportant. If you look at the exams for the past three years and see that there is not a single question on common nomenclature, but there are tons of reagent questions, take the hint: Study reagents.

One trap that many students fall into is getting comfortable after they do well on the first exam. Don't fall for this trap. The first exam is quite often the easiest exam you'll take all semester. Organic chemistry is a marathon, not a sprint. You have to pace yourself, so set a little bit of time aside each day when you do organic chemistry come rain, shine, or big frat party — and don't let up.

Study the Right Way

Learning organic chemistry is not a passive task. You can't just read the book and expect to soak up the material, like water into a sponge (although some students have tried using the text as a pillow, just in case). You have to actively engage yourself, working the problems in the text of the chapters as you go along, underlining key passages (don't worry about marring your book), and working the problems at the ends of the chapters. Some students outline the chapter as they putter through it, emphasizing all of the critical ideas that can be used while simultaneously making a crib sheet for when you prep for an exam.

Don't attempt to memorize your way through the course. It won't work, you'll quickly become frustrated, and you'll waste a lot of time. In organic chemistry, you have to learn and genuinely understand the concepts and then be able to apply them. Many students, I think, don't take this idea to heart right away because the word "learn" is so often used as a euphemism for "memorize" by college professors. But this time your professor really means that you

need to completely understand the material. Sure, organic chemistry involves memorization. Anyone who says there isn't memorization in organic chemistry is lying to you. Yet there are millions upon millions of organic molecules, and millions of specific reactions, so you need to comprehend the generalities and be able to apply these general concepts to any problem.

Go to Class

This tip is probably a no-brainer, but it's still an important one. Different professors emphasize different things, and you won't know what they think is particularly important (or unimportant) unless you go to class. Some professors are sticklers for nomenclature, and others don't give two bits about it as long as you understand the basics. Some want you to memorize the pKa tables, some won't. You'll never know if you don't show up. In class, professors often let slip valuable information about what's going to be on exams. Whenever they say something like, "expect a question like this to show up on the exam," put a big star near it in your notes, double underline it, and emphasize it with a highlighter. They probably meant it.

Going to class is also an efficient use of your time, because a good professor does a better job of explaining organic chemistry than a textbook can. In other words, an hour in class is worth two on your own. Of course, the time you spend in class will be much more fruitful if you have read the textbook *before* going to class. Sitting in class and brainlessly copying notes off the chalkboard without having a clue of what your professor is talking about is a waste of your time. So reading your textbook beforehand will allow you to get the most out of your time in class. Class time is also a good time to ask questions about concepts you had difficulty understanding when you read the book.

Get Help When You Need It

Professors have office hours and so do teaching assistants. Your tuition pays their salary, so make use of them. If you get stuck on a problem (and everyone will at some point) or you just don't understand a concept, go see one of them. They'll probably be happy to help you (unless it's after 5 pm on Friday, when they just want to leave and get a beer during Happy Hour). If you think you're going to need consistent one-on-one help, ask your professor about finding a tutor.

Ask Questions

Don't fall for that claptrap that says you'll look stupid by asking a question. Organic chemistry is not an obvious subject (and that's an understatement). Believe me when I say that after a couple of weeks, over half the students in your class will be utterly lost and will have absolutely *no* idea what the professor is jabbering on about (you, of course, will understand because you read the chapter before you went to class). So for you not to understand an idea here or there is a minor issue, and is certainly nothing to be ashamed about.

Believe it or not, professors *like* students who ask questions. Questions from students let professors know what topics they need to explain better and how they can improve their teaching. Asking questions also lets your professor know that you're actively engaged in the class, and when the end of term rolls around with your grade hovering near a grade cutoff, your professor may decide to give you the old heave-ho to the higher rung because you demonstrated in class that you put in some effort.

Do Organic Every Day

Cramming organic chemistry is an exercise in futility. It just won't work. You've got to practice it a little every day to master it. Plus, you need a fresh brain to take an organic exam, not one fatigued from caffeine-fueled all-nighters when you pored despairingly over your piles of textbooks, notes, and homework, cursing Friedrich Wöhler's name for laying the foundation that is modern organic chemistry.

Believe me, I *tried* it this way a couple of times when I took the class (and so will half of your classmates, most likely). It just doesn't work. You have to do organic faithfully every day. If you have a good advisor, then you won't have signed up for multivariable calculus, differential equations, quantum physics, and advanced programming in C++ in the same semester that you're taking organic, and you'll have some time to devote to organic every day. Take an easier course schedule — avoid overloading with classes that end with the suffix *-ology* or *-ics* while simultaneously taking o-chem. Later in the semester you'll be thankful for this breathing room.

Take Exams the Right Way

Working exams sequentially is easy enough in most classes, starting with the first question and proceeding with each subsequent question in order. But organic isn't like most classes because time is so often a factor. It's a common sight to see organic students coming out of an exam frustrated because they didn't finish. To make the best use of your time, scan through the test quickly when you first get it, and then answer all of the easy questions first. After you've answered the easy ones, go back and work the harder ones. Don't allow the time to run out with easy questions on the last page still unanswered because you spent 20 minutes battling that humdinger of a question on page two.

Most importantly, read each question on the exam. Don't just assume that you know what a professor is asking. This tip is pretty basic, but many students don't read the questions carefully and lose points for neglecting to answer the question the way the professor wanted, or for not answering a part of the question. You want all of the points you can get, so don't fritter any away by making a silly mistake like forgetting to read the question.

Another mistake to avoid is being unclear in your answers. Organic exams often include questions that require some explanation , and graders — alas! — are not mind readers. Make sure that you have explained every portion of the question clearly. Put yourself in the shoes of the grader and think, "Would I understand what I'm saying here?" Don't leave anything to subtext. You'll have a hard time trying to win back points on a regrade when your explanation to your professor starts with the words, "But what I meant was . . ." Make your answer clear.

Have confidence in yourself and your abilities. Try to avoid second-guessing yourself on every question. If I had a quarter for every time a student told me he or she had answered a question correctly, listened to the infernal whisperings from the creature of doubt perched on his or her left shoulder, and then erased the right answer and penned in the incorrect one, I'd have enough money for that house of gold I've always wanted (or at least the first down payment). Also, never leave a question blank. Many professors give out partial credit (and sometimes even "pity points" if you just make a stab at a question), so it can't hurt to at least make an educated guess.

Work the Problems

This point can't be overemphasized. You can't do well in organic chemistry unless you work the problems. So, work the problems! Work the problems! Work the problems!

Chapter 19

Ten Cool Organic Discoveries

In This Chapter

- Seeing ten important discoveries in organic chemistry
- Recognizing the role that serendipity plays in the discovery process

In this chapter, I cover ten cool discoveries that relate to organic chemistry. One interesting feature of this list is that all of these discoveries contain some element of the serendipitous. Although you can never discount hard work and preparation, chance and fortune have played a major role in the big discoveries in organic chemistry (although, as Pasteur would say, luck favors the prepared mind).

Explosives and Dynamite!

Alfred Nobel and his family recognized the potential of nitroglycerin as a commercial explosive — a substance with explosive properties more favorable than gunpowder. In his laboratory, however, his family discovered firsthand how dangerous the substance could be. In a massive nitroglycerin explosion, Alfred's brother Emil and several co-workers were killed.

After the accident, Alfred worked to make nitroglycerin safer (see Figure 19-1). He noticed that when he mixed the syrupy nitroglycerin with silica powder (diatomaceous earth) he obtained a stable mash that he called dynamite. When he commercialized his discovery — along with blaster caps to safely start the explosion — he became one of the wealthiest men of his time. When he died in 1896, he left his fortune to set up the Nobel Foundation. Each year, the Nobel Foundation grants the prestigious Nobel Prizes, of which, ironically, the Peace Prize is one of the most famous.

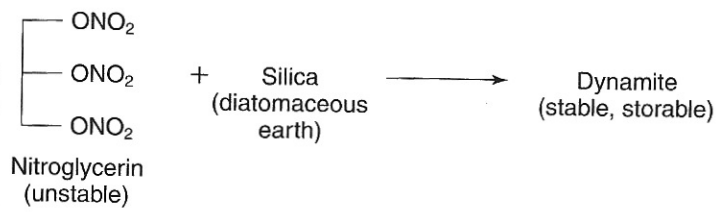


Figure 19-1: Making dynamite.

Fermentation

No one knows for sure who discovered fermentation, but fermentation was probably first observed many thousands of years ago in caskets of rotting fruit. After being bruised and left out for several weeks, fruit *ferments* (gets broken down by enzymes in yeasts) to make alcohol, as shown in Figure 19-2. Although this rotting fruit probably didn't taste very good, someone who drank the juice discovered that it had a potent and pleasurable effect on the body. This likely led to the discovery of wine making, and, some time later, beer making, which uses grains and honey as the source of sugars and carbohydrates rather than fruit.

The Sumerians are the first on record to begin brewing beer, some 6,000 years ago (although beer making probably was going on long before this time). In fact, some have suggested that many humans gave up their nomadic lifestyles and became farmers after the discovery of fermentation, just in order to grow crops to make beer. (This suggestion seems to coincide with human nature.)

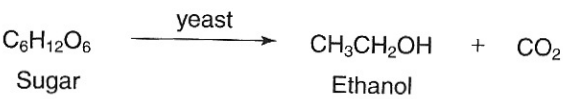


Figure 19-2: Making alcohol.

The Synthesis of Urea

The synthesis of the organic compound urea from an inorganic substance by Friedrich Wöhler was one of the first major breakthroughs in organic chemistry. With this accomplishment, he showed that organic substances were not held together by a "vital life force," as had been postulated at the time.

Wöhler had attempted to synthesize ammonium cyanate as a continuation of his studies of inorganic cyanates. He isolated instead a substance that seemed to resemble urea, "a so-called animal substance," or in modern terms, an

organic compound. See Figure 19-3. Comparing the properties of his synthesized compound to those of the pure urea he had extracted from urine, he found that the properties of the two were identical.

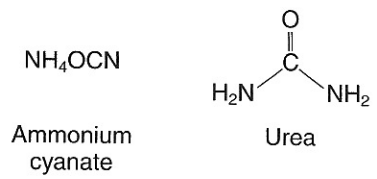


Figure 19-3: Wöhler made urea from ammonium cyanate.

The Handedness of Tartaric Acid

The handedness of tartaric acid (shown in Figure 19-4) was discovered by Louis Pasteur. Why was Pasteur studying tartaric acid? As a French chemist, he was studying wine (of course), of which tartaric acid is a component. He noticed that tartaric acid formed into two different crystal shapes. He separated the crystals with tweezers under a microscope, and noticed that crystals of one shape rotated plane-polarized light in one direction, and the other crystals rotated light in the opposite direction. He surmised (correctly) that these different crystals must relate to the handedness of the molecules themselves.

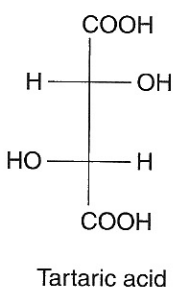


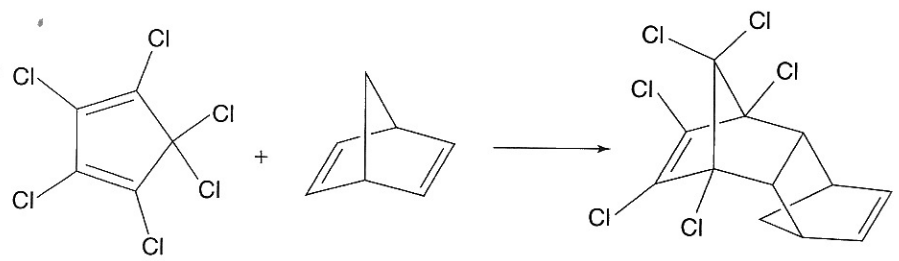
Figure 19-4: Tartaric acid.

not

Diels-Alder Reaction

Two German chemists, Otto Diels and Kurt Alder, discovered the diene synthesis currently known as the Diels-Alder reaction. This reaction is just cool — it forms two carbon-carbon bonds simultaneously, and is extremely useful for the construction of strange-looking bicyclic molecules, like the pesticide Aldrin shown in Figure 19-5, and various six-membered rings.

Interestingly, in their classic paper describing the reaction, Diels and Alder wrote, "we explicitly reserve for ourselves the reaction developed by us to the solution of such problems [natural product synthesis]." Surprisingly, this "back off!" warning to other chemists had the desired effect: Other chemists stayed away from this reaction until after WWII was over, and synthetic chemistry in Germany had taken a serious hit. Typically, though, such statements in the literature have the opposite effect than the intended one. Moses Gomberg found this out the hard way in 1900 when he reserved for himself the right to study the triphenyl methyl radical ($Ph_3C\cdot$) — the first radical known to chemists — and chemists trampled over each other to begin their own research on the molecule.



Aldrin (an insecticide)

Figure 19-5: Making Aldrin with the Diels-Alder reaction.

Buckyballs

Buckyballs are the most recently discovered allotrope of carbon. *Allotropes* are compounds that contain only a single element — in this case, carbon. Other carbon allotropes include graphite and diamond. Buckyballs, discovered in 1985 by Richard Smalley, Harry Kroto, and Robert Curl, look like molecular soccer balls. Buckyballs were discovered accidentally when these chemists blasted a laser at graphite powder, and passed the products through a mass spectrometer. They noticed a peak in their mass spectrum that corresponded to exactly 60 carbons. Using intuition, they surmised that the structure corresponding to this peak must be a spherical molecule (see Figure 19-6). They named this molecule buckminsterfullerene, after Buckminster Fuller, who popularized the geodesic dome; because of their spherical shape, these molecules are often called *Buckyballs*. Although these molecules have not produced any practical applications so far, they're being studied for use as superconductors, as gasoline markers (so oil spills can be traced back to a specific oil company), and as vehicles for drug-delivery.

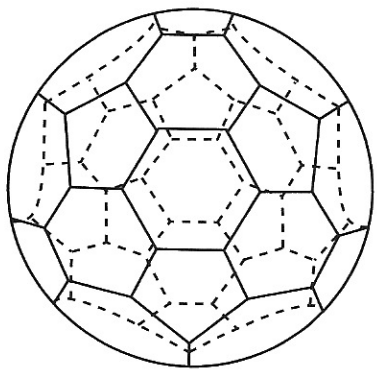


Figure 19-6: Buckyball.

Soap

Legend has it that soap was first discovered by Roman women washing their clothes along the Tiber River. They noticed that in some places of the river their clothes got cleaner than when they washed them in other places. Apparently, next to the river was a sacrificial site, where, presumably, the animal fat from the sacrifices mixed with the fire ashes (which contain lye, or sodium hydroxide), making soap (see Figure 19-7). The soap then ran down the hill to the river after it rained.

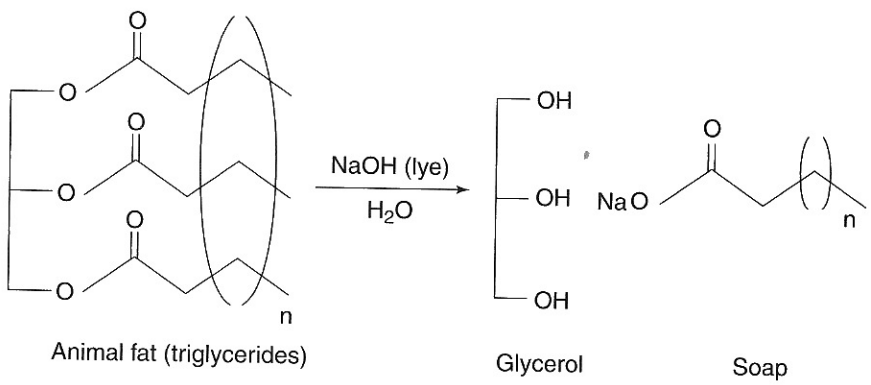


Figure 19-7: Making soap.

Aspartame

James Schlatter discovered aspartame by doing something that would make safety experts cringe — he licked his fingers after working in the lab. He found that his fingers tasted very sweet. He traced back the sweetness to aspartame

(shown in Figure 19-8) the compound he was working on (and he had another taste of his synthetic aspartame just to be sure he was right). And so was born one of the most popular sugar substitutes. Nutrasweet and Equal all contain the sugar-substitute aspartame, as do many diet soft drinks.

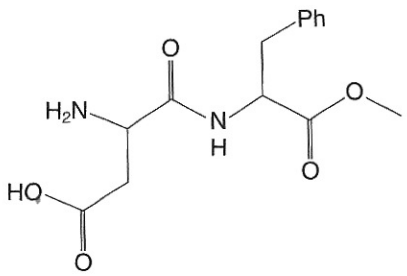


Figure 19-8: Aspartame.

Penicillin

The story of penicillin's discovery is probably the most well-known case of serendipity in the discovery process. Alexander Fleming was doing research on *Staphylococcus* bacteria, when he noticed that his culture plates had become contaminated by a *Penicillium* fungus. He discarded the plates into a sterilizing wash, but didn't submerge them properly. When he returned to the lab, he noticed that on the plates where the fungus had grown, the bacteria had been killed. "Something that the fungus is producing must be killing the bacteria," he thought to himself. That something was penicillin (shown in Figure 19-9), an antibiotic that would eventually save countless lives.

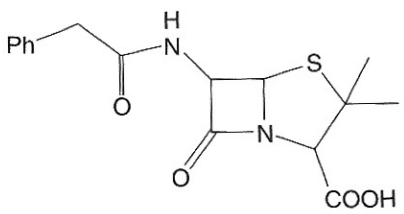


Figure 19-9: Penicillin.

Teflon

Two chemists, James Rebok and Roy Plunkett, who worked for Dupont, discovered Teflon in 1938. Teflon is the polymeric nonstick surface that keeps your eggs, bacon, and pancakes from sticking to your frying pans (see Figure 19-10

for the structure). When they discovered Teflon, Rebok and Plunkett were working with fluorinated hydrocarbon gases kept in large canisters. One day they opened the valve on what they thought was a full canister of gas, but no gas came forth. At first, they thought that the canister had sprung a leak, until they noticed that the supposedly empty canister had the same weight as a full container. Sawing open the container, they found a sticky white substance had coated the inside of the container — Teflon!

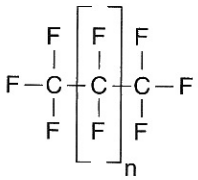


Figure 19-10: Teflon.

Chapter 20

Ten Great Organic Chemists

In This Chapter

- Introducing ten pioneers in the field of organic chemistry
- Finding out about discoveries that transformed organic chemistry

Although this is a list of ten (or so) great organic chemists, only one woman — Dorothy Hodgkin — is on the list. This exclusion is not a snub of female chemists, but simply a reflection of what has been until recently a male-dominated industry. The work of these ten chemists (eleven, actually) reflects the diversity of organic chemistry, and is work that's made a significant impact on the field (or, in the case of Linus Pauling and John Pople, shook the trunk of chemistry, not just the branch of organic chemistry). Some of these folks are those who pioneered organic chemistry back at the turn of the twentieth century and before, and some are people who are still plugging away today, making further contributions to the field of organic chemistry.

Robert Burns Woodward

Many claim that Woodward was the greatest of all organic chemists — and certainly, a case can be made for that claim. Prominent among his many accomplishments were his syntheses of astoundingly complex organic molecules such as Vitamin B_{12} (in collaboration with Albert Eschenmoser), strychnine, and quinine (see Figure 20-1). These syntheses are particularly magnificent considering that they were performed at a time when spectroscopy and structure determination were a shadow of what they are today. (In fact, Woodward pioneered several spectroscopic techniques for structure elucidation.) Along with Roald Hoffman, Woodward solved the puzzle of why pericyclic reactions (like the Diels-Alder reaction in Chapter 12) occur in the manner they do; he did so by using arguments about orbital symmetry, a formulation now called the Woodward-Hoffman rules (which you may learn about if you take the second semester of organic chemistry). He won the Nobel Prize in chemistry in 1965 "for his outstanding achievements in the art of organic

synthesis" and would have undoubtedly won the prize again along with Roald Hoffman for the Woodward-Hoffman Rules had he not died two years earlier. (Nobel Prizes are not awarded posthumously.)

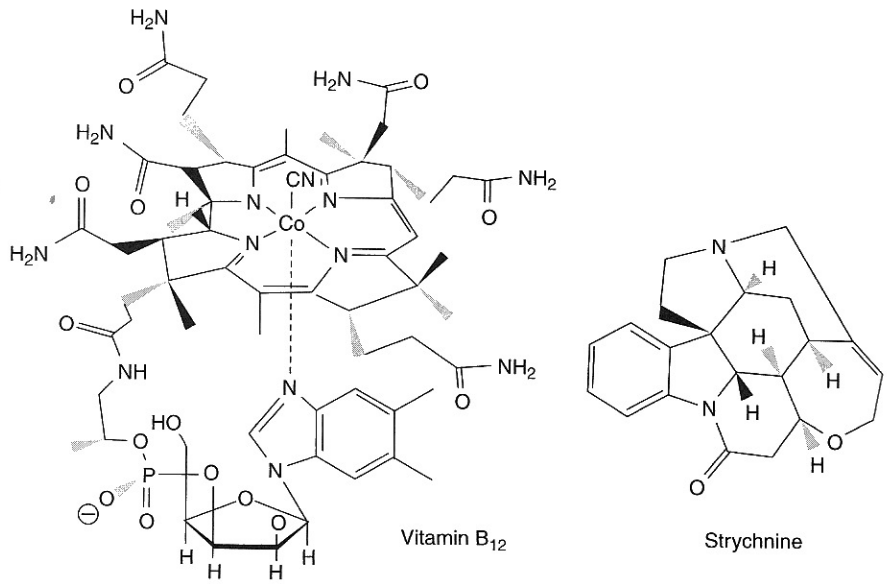


Figure 20-1: The structures of Vitamin B_{12} and strychnine, two of Woodward's grand synthetic achievements.

August Kekulé

By some accounts, August Kekulé was a bore as a lecturer and a klutz in the lab, but his ideas on the nature of organic compounds were extremely influential (and, more importantly, correct). He proposed, correctly, that carbon could make four bonds to other atoms, and could form complicated structures by combining with other carbon atoms to make chains and rings. Kekulé also proposed the correct structure for benzene, C_6H_6, and notoriously bragged years after the fact that his inspiration for the cyclic structure of benzene came from a dream he had of a snake biting its tail, a claim as suspect as it is entertaining.

K.C. Nicolaou

K.C. Nicolaou is another giant in the field of synthetic organic chemistry. His synthetic accomplishments include the total synthesis of taxol, brevetoxin B, and calicheamicin. Calicheamicin, shown in Figure 20-2, is a remarkable

antitumor compound that contains an ene-diyne portion (an alkene flanked by two alkyne units) crucial to the compound's activity. The molecule binds to a groove in the tumor cell's DNA, then snips through the DNA like scissors through paper, destroying the DNA and ultimately killing the tumor cell. (You can read more about the origins and biological activity of calicheamicin in Chapter 6.) Nicolaou's two books on synthesis — *Classics in Total Synthesis and Classics in Total Synthesis II* — are must-reads for anyone interested in synthetic chemistry.

Stepping back and looking at such complex natural monuments as calicheamicin and vitamin B_{12} — and thinking about what great accomplishments their syntheses were — may make you less inclined to gripe about the comparatively simple syntheses you have to consider in undergraduate organic courses. (Well, perhaps you're still not happy about synthesis problems, but even so, these structures are pretty awe-inspiring.) Nicolaou currently works at Scripps Research Institute in California.

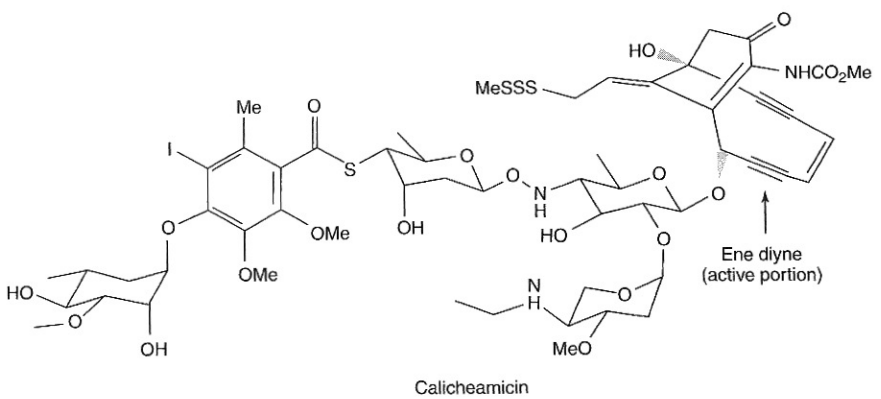


Figure 20-2: The structure of calicheamicin.

E. J. Corey

E. J. Corey was the first to clearly articulate the art of organic synthesis, and showed that retrosynthesis — the technique of working backward from a target molecule — was the most viable strategy in planning the synthesis of a complex molecule. Along with R. B. Woodward, Corey elevated the synthesis of complex organic molecules into an art form. Recently, Corey claimed publicly that he inspired Woodward to think about orbital symmetry in pericyclic reactions (which led to the Woodward-Hoffman Rules) and suggested that he deserves credit for this significant accomplishment. Hoffman, however, has dismissed his claim. Regardless of whether he deserves credit for this

achievement (with Woodward dead, we may never know whether he does or not), Corey elevated the stature of organic synthesis, and he was justly awarded the Nobel Prize in chemistry in 1990 for defining retrosynthetic analysis.

Louis Pasteur

Louis Pasteur discovered the handedness of organic molecules — the fact that molecules can have the same atomic connectivity but different orientations of those atoms in space. Pasteur made this discovery by observing that tartaric acid formed into two distinct types of crystals. He then separated the two types of crystals with tweezers under a microscope and noticed that *plane-polarized light* (light that oscillates in a single direction) rotated in one direction when it passed through one type of crystal, and in the opposite direction when it passed through the other type of crystal. With these observations, he speculated that this difference in crystal shape and light rotation must relate to different orientations of the atoms in the two crystals. He was right, and the foundation for our current understanding of stereochemistry was laid.

Dorothy Hodgkin

Dorothy Hodgkin became involved in structure determination using a technique called x-ray crystallography. Although she suffered from severe health problems, including crippling arthritis, she was extremely persistent and hard working, and determined the structures of many important molecules using x-ray crystallography, including the structure of penicillin and, later, the structure of vitamin B_{12}. She won the Nobel Prize in chemistry in 1964 for her work.

Emil Fischer

Fischer was one of the pioneers in organic chemistry. After being told by his father that he was too stupid to be a businessman, he attended the University of Bonn and studied science. After receiving his doctorate, he worked at the University of Munich. Fischer worked on synthesizing and determining the structures of sugars, and discovered the d/l stereochemistry of sugars. He then made significant advances in the understanding of purine nucleotides

(adenine and guanine, two of the DNA bases, are purine nucleotides). While the beginning of his career was marked by creative genius, his life ended in tragedy. He suffered from the side effects of the toxic mercury compounds he worked with in the laboratory, and when his wife died, and shortly thereafter two of his three sons were killed in the First World War, he committed suicide. Though his life ended in tragedy, his accomplishments in organic chemistry are considered some of the finest by an organic chemist.

Linus Pauling

Linus Pauling used quantum mechanics to describe the nature of chemical bonds and how atoms come together to form molecules. His book, *The Nature of the Chemical Bond,* is considered a classic in the field. After his theoretical work on chemical bonding, Pauling pioneered the field of chemical biology and elucidated the structures of proteins.

Pauling was an unusual person. He advocated taking massive daily doses of Vitamin C, and he was so vocal against government policies that he was denied visas to attend major international science conferences. Some have suggested that had he attended a conference in which Rosalind Franklin presented her x-ray structures of DNA, with his understanding of helices from his work on proteins, he may have elucidated the structure of DNA before Watson and Crick (who attended the conference). Pauling is the only person to win two unshared Nobel Prizes — one in chemistry, for his insights into the nature of the chemical bond, and the other in peace, for his uncompromising stand against nuclear testing and proliferation. Pauling died in 1994 at the age of 93.

John Pople

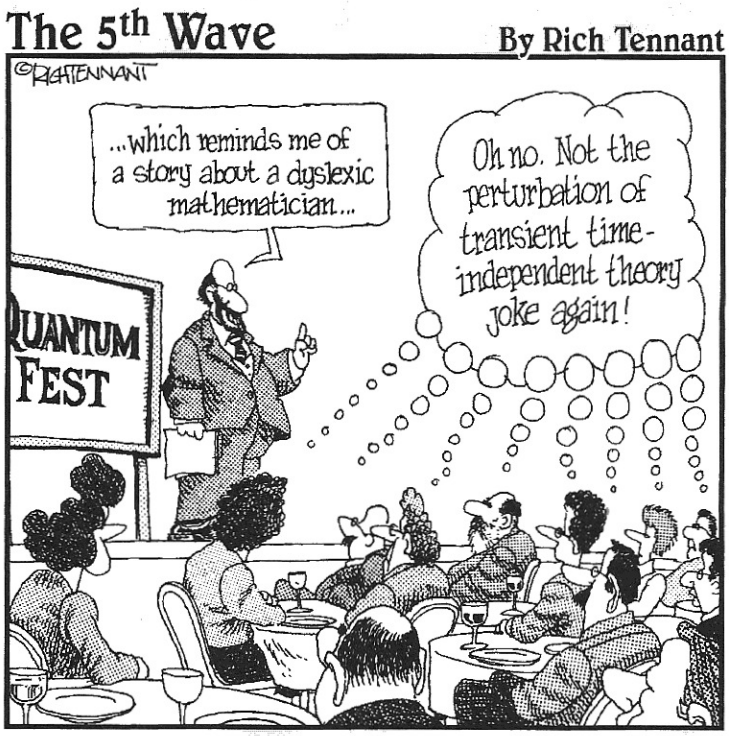
John Pople made practical the use of computational techniques. He took theoretical chemistry out of the ivory tower and placed it into the hands of practical wet chemists. He made theoretical calculations available to even the novice chemists, whereas before they had only been available to the hard-core theoreticians with degrees in mathematics. He was the pioneer of the computational program Gaussian, a user-friendly computer software program designed to carry out these molecular calculations. He shared the Nobel Prize in chemistry for his development of computational methods. He died in 2004, after a career that spanned almost an entire century.

Friedrich Wöhler and Adolf Kolbe

Friedrich Wöhler and Adolf Kolbe laid the foundation for modern organic chemistry by unseating the established theory of vitalism, the theory that organic molecules contained a vital life force not present in inorganic compounds. By synthesizing the organic molecule urea from inorganic ammonium cyanate, Wöhler disproved the theory of vitalism. Even after this experiment, however, many chemists were still skeptical.

Wöhler's pupil, Kolbe, dealt the deathblow to vitalism when he synthesized acetic acid from materials that could be made directly from the elements. Great deeds, however, are not always done by the nicest of people. It seems from his own writings and accounts of him by others that Kolbe was something of a jerk, and an anti-semite who hated the French. "The French are truly a nation of half children, half madmen," he wrote. "I have had a deep hatred and contempt for the French, but I had never considered them so uncivilized, barbarous, and base as we now see them to be." Despite being xenophobic and something of an unpleasant man, his accomplishment in toppling vitalism is undeniable.

Part VI
Appendixes



In this part . . .

I give you guides on how to work through multistep synthesis and mechanism problems, because these kinds of problems are ubiquitous through organic chemistry and are particularly challenging to most students. I also include a chemical glossary to help you keep all the terminology straight.

Appendix A

Working Multistep Synthesis Problems

In This Appendix

- Understanding multistep synthesis problems
- Discovering tips for working multistep synthesis problems

Multistep synthesis problems are prevalent throughout organic chemistry — and they tend to show up more and more frequently as the course goes on. Many students cite these problems, along with mechanism problems, as the most difficult types in the course. This appendix details why people bother with multistep synthesis and gives several commandments for how to work these kinds of problems so that you can avoid committing the major multistep synthesis sins.

Why Multistep Synthesis?

A good illustration of the importance of organic synthesis is drug making. Throughout history, drugs have primarily been obtained from natural sources. The kings of Mesopotamia smoked poppy flowers to get high on the hallucinogenic properties of the opium alkaloids, Native Americans chewed aspirin-containing willow bark for pain relief, and Fleming discovered penicillin in a mold that grew on his *Staphylococcus* bacteria plates. Even today, natural product chemists extract compounds from living things, characterize them, and test them to see if those compounds have biological activity.

But extracting drugs from natural sources has its problems. Oftentimes, the drug comes from a source that's rare (like an exotic plant or fungus), and sometimes from a source that's endangered or near extinction. The extraction of these compounds can also be challenging, because the active compound must be separated from the mass of inactive molecules; this can be a difficult task in some cases.

Sometimes the source doesn't produce the drug in high quantities, and starting with thousands of pounds of a source material and extracting just a few paltry milligrams of the desired compound from it is not uncommon. Nature may be a far better synthesizer of organic molecules than humans can ever dream of becoming, but that doesn't mean that nature produces the needed quantities of material on demand. Taking thousands of pounds of a species on the verge of extinction to make just a few small doses of a drug is usually impractical.

So how can chemists get the desired compounds? By multistep synthesis. This process involves making the compounds from scratch. To do so, chemists take commercially available starting materials and build up the desired molecule using available reagents and techniques. A great many of the drugs that you can buy from pharmacies today were made by multistep syntheses, using enormous quantities of starting materials and reagents that were added with front-end loaders into gigantic reaction vessels. But all of that was first planned out on paper by chemists, plotting the shortest, cheapest, and most elegant route available to the target compound (with the shortest and cheapest routes taking precedence in the pharmaceutical industry, and elegance being prized in academia).

Of course, that doesn't mean that the application of multistep synthesis is limited to drugs. Multistep synthesis is used for many different purposes, and one advantage of the organic chemist's ability to make compounds is the free reign this ability gives him or her to do pretty much anything in chemistry (which is why biochemists and physical chemists are forced to collaborate with synthetic organic chemists if they want to get anything done). In some cases, multistep synthesis is even carried out for the sake of synthesis itself. In these cases, organic chemists synthesize structurally interesting natural products that have *grant proposal activity* — that is, products that may show enough biological activity to fund a grant proposal, but likely do not have enough potential to be considered for clinical trials. In these cases, multistep synthesis is used as a framework to develop new reactions, as a way of testing known reaction methods, and more generally as a stomping ground for chemists to flaunt their synthesizing prowess.

And although synthetic chemists do their best to plan the syntheses of complicated molecules, steps invariably go wrong when trying them out in the laboratory. This failure is often a good thing, however. When planned reactions in a synthesis don't work, organic chemists need to figure out new ways of doing things to get around the barriers that these molecules put up. Often, new reactions and insights are discovered in this way.



For example, the synthesis of Vitamin B_{12} (discussed in more detail in Chapter 20) was carried out knowing ahead of time that any synthesis of this extremely complex molecule would be too expensive to perform on a commercial scale. Still, the synthesis of this molecule was extremely valuable to organic chemists. Many new synthetic techniques were discovered during this synthesis, in addition to one major theoretical breakthrough (understanding pericyclic reactions like the Diels-Alder reaction) that occurred while contemplating one of the steps in the reaction. So while this synthesis of Vitamin B_{12} was too impractical to carry out on a commercial scale, the total synthesis of this molecule added a great deal of knowledge to the field of organic chemistry.

The Five Commandments

Multistep syntheses are the kind of problem in which you're told what the starting material and the product are, and you're asked to figure out a synthetic route that'll convert the starting material into that product. For these types of problems, you must provide reagents to convert the starting materials into one or more intermediate compounds that you'll then further react in order to make the final product. Often, there will be several steps in the synthesis. However, *no mechanisms (arrow pushing) need to be shown for the individual reactions in a multistep synthesis problem.* This is a common mistake. For these problems, simply provide the reagents and the products of each step as you go along.

For example, suppose the question asked how to convert Compound W into Compound Z (see Figure A-1) using multistep synthesis.

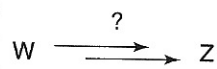


Figure A-1: Multistep synthesis.

Here, an acceptable answer would show the individual reactions that would transform Compound W into Compound Z (an example is given in Figure A-2). Note that no mechanisms for these reactions are shown, just the reagents and the intermediates along the way. In many cases, more than one route is possible for the conversion of the starting material into the product, so these types of problems often have several acceptable answers (the shortest route is often preferable, however).

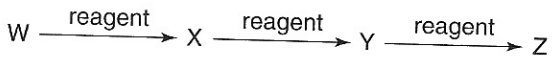


Figure A-2: Answering multistep synthesis questions.

Here are five commandments to help you solve these synthesis problems.

Commandment 1: Thou shalt learn thy reactions

Learning the reactions is the most basic requirement for multistep synthesis. No matter how smart you are, you don't stand a chance of getting synthesis questions right unless you know the reactions. Memorize the reagents, use flash cards, or use whatever other techniques you find most helpful, but learn the reactions cold. This memorization is not something that you can do overnight. Learning the reactions takes time. A good technique is to add reagent learning as a portion of your daily study time.

Because organic chemistry is a cumulative course, you can't afford to forget any reactions that have been covered in previous chapters. If you use flash-cards (a method I highly recommend), you should never throw away your stack of old flash cards that contain the reactions from previous chapters. Instead, keep adding to your pile (yes, the deck will be thick enough to choke a whale by the end of the course!). Most textbooks have convenient end-of-chapter reaction summaries that give an overview all of the reactions that were covered in the chapter, and these overviews can be extremely helpful in making flash cards.

Commandment 2: Thou shalt compare carbon skeletons

The first thing to look for in a multistep synthesis is to compare the carbon skeleton of the starting material to the carbon skeleton of the product. Were any carbons lost or added? If so, can you identify where they were added or lost? A count of the number of carbons in the reactant and the product doesn't take long, but can help you determine what kinds of reactions you're dealing with.

Take the following simple example shown in Figure A-3. The lighter-shaded portion of the molecule identifies where the likely carbon skeleton of the reactant is found in the product. Looking at the molecules in this way allows you to clearly see what portion needs to be added or lost during your synthesis. (This step may seem trivial in this obvious example, but in tougher problems, this process can help you organize your thoughts.)

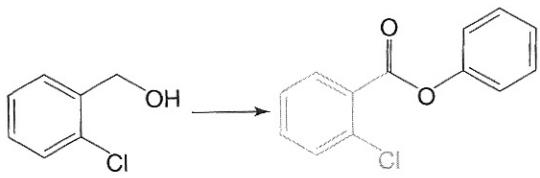


Figure A-3: Comparing carbon skeletons.

Commandment 3: Thou shalt work backward

Have you ever worked through mazes and found that you can more easily get through a maze by starting at the finish and working back to the start than you can by working from the start? The same thing applies to multistep synthesis problems. Working backward in synthesis problems is a technique termed *retrosynthesis.*

The first thing you want to look at is your product, thinking of all the reactions that you know of that could form it. For the moment, ignore your starting material. If your product is an alkene, for example, think of alkene-forming reactions like elimination reactions or the Wittig reaction. (See Chapter 8 for a summary of alkene-making reactions.) Write all of these reactions out and look at what reactant would be required for each.

After you've written out all of the potential reaction candidates, return to your starting material. Which reaction has a reactant that most resembles your starting material? That one is probably the best one to select as a potential candidate.

For example, suppose you were asked to do the synthesis shown in Figure A-4.

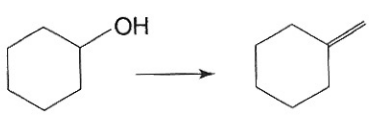


Figure A-4: Sample synthesis problem.

After completing the first two commandments, you would want to think of ways to make the alkene in the product. Ignore the starting material for the moment. Just brainstorm all of the ways you can think of to make the alkene and write them down on your scratch paper. You should get something that looks like the following list (see Figure A-5).

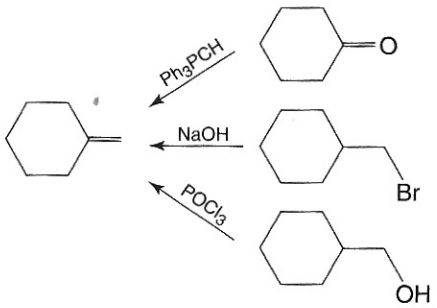


Figure A-5: Alkene-forming reactions.

Now you have three possible routes to choose from. The route to choose is the one that uses a reactant that most resembles the original starting material. If you did step 2 (accounting for the carbon skeleton), you would know that the product has one carbon more than the starting material. Only the first reaction, the Wittig reaction, accounts for this additional carbon, so the Wittig reaction would be the reaction you would tentatively choose. If this choice turns out to be wrong, you can always go back and try another route.

Looking at the reaction scheme, you now have something that looks like the following reaction (see Figure A-6).

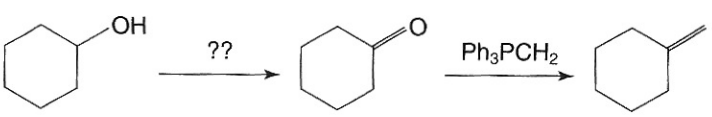


Figure A-6: Completing a retrosynthesis.

Now repeat the same procedure for cyclohexanone, thinking of all the different ways you could make this ketone. One pointer here is that the closer you get to completing a retrosynthesis — in other words, the closer you get back to your starting material — the more you should reference the starting material in your thinking. At this point, for example, you may want to modify your thinking from, "I need to think of all the ways I can make cyclohexanone," to perhaps something more like, "I need a reaction that converts an alcohol to

a ketone." If you did step one, you would know several ways of producing a ketone from an alcohol (for example, using Jones' reagent, PCC, and so forth.) Choosing one of these methods would complete your synthesis.

If you get stuck, go back and try one of the other pathways. If the Wittig reaction in our example had lead to a dead end, then you could have gone back and tried one of the elimination reactions. Choosing the correct way back is often a matter of intuition, and that only comes after working a lot of problems (see Commandment 5).

Commandment 4: Thou shalt check thyne answer

After you have a potential synthesis, go back and make sure that all of your reagents are compatible with the functional groups on your molecule. Make sure, for example, if you're proposing a Grignard reaction, that there are no alcohols or other incompatible functionalities on your reagent. Undergraduate organic professors often seem to take delight in creating challenging (tricky) exam questions, so double-check every detail of your synthesis for correctness.

Commandment 5: Thou shalt work many problems

This is the greatest commandment of all. As a mere mortal, you have no way around this; you have no magic formula at your disposal to avoid this commandment. A good textbook will have plenty of multistep synthesis problems to practice on. Start with easy synthesis problems to get the feel of what's required, and then work your way to harder problems.

If you have a solutions manual to your text (something that I highly recommend you have), don't refer to it until *after* you've completed the problem. Just as it would be unreasonable to expect to be able to play the piano after only listening to someone else play and without ever practicing yourself, you can't expect to look at the study guide and be able to do synthesis problems on the exam without ever having practiced these problems by yourself. Looking at the solution manual and thinking, "yeah, I could do this problem," is no substitute for actually doing that problem. You need experience. Get lots of experience!

Appendix B

Working Reaction Mechanisms

In This Appendix

- Defining mechanism problems
- Seeing the do's and don'ts of mechanism problems
- Distinguishing mechanism from synthesis questions
- Seeing common mistakes in drawing mechanisms

Organic chemists want to know *what* reagents convert one kind of molecule or functional group into another. But they also want to know *how* reactions happen. They want to know what exactly happened when they threw different chemicals into a flask that converted the starting materials into the product. If organic chemists know how a reaction happens, they can more easily optimize reaction conditions (the solvent, temperature, acidity, reagent amounts, and so on) that allow the reaction to proceed most efficiently. The mechanism of a reaction shows how a reaction takes place.

By understanding the mechanism of a reaction, chemists also get a better understanding of how reactions work, and they're better informed about when a new reaction is likely to succeed or fail. A reaction mechanism is the detailed stepwise process that uses arrows to show how electrons moved during a reaction. A complete mechanism includes all of the bond-making and -breaking steps that convert the starting material into product, and shows any intermediate species formed along the way.

The Two Unspoken Mechanism Types

From a very pragmatic standpoint, in organic chemistry you see two unspoken classes of reaction mechanisms — those reaction mechanisms that you can figure out on your own, and those that you simply have to memorize. If you're taking a typical class in introductory organic chemistry, you will likely see an abundance of both types. The bromination reaction of alkenes (see Chapter 8), for example, is a reaction mechanism that you simply have to memorize. You'd

have a very hard time figuring out on your own that the reaction mechanism involves a three-membered bromonium ion intermediate. The existence of this intermediate may even have come as a surprise to the researchers who discovered the mechanism!

Because you simply have to commit these kinds of mechanisms to memory, I can't do much to help you to learn them, except to show you the mechanisms when discussing the reactions in this book, and to give you tips on how to study effectively (see Chapter 18). Where I *can* help you is in understanding the mechanisms that you can work out on your own, and in arming you with general principles for reactions whose mechanisms are not found in the text.

I think that one reason students have problems with mechanisms problems is that they don't see this distinction between mechanisms that they need to memorize — which are often impossible to figure out independently — and mechanisms that they need to be able to work on their own. Many look, for example, at the bromination reaction and, knowing that they have to be able to work out mechanisms for themselves, pour ashes on their heads and rend their garments and think, "I could never figure that out on my own!" They then become discouraged about the whole business, even though bromination is not a mechanism that students are expected to be able to deduce on their own.

Still, even if this distinction is understood, most students find these work-it-yourself mechanism problems quite challenging. These problems are challenging for two reasons. First, unlike the mechanisms you need to commit to memory, memorization is useless and impossible with the kinds of mechanism problems you're supposed to be able to work out on your own. Second, professors think that asking students to draw the mechanisms for reactions they've never seen before is perfectly reasonable. The trick for working mechanism problems is to understand the general principles of arrow pushing (see Chapter 3), and to get lots of practice (lots and lots of practice!). I detail some of the general principles here, and give you some tips on good mechanism-writing habits. I also show you some common pitfalls to avoid when writing mechanisms. I then go through an example mechanism to illustrate how these principles can be applied to a real problem.

Do's and Don'ts for Working Mechanisms

Knowing what not to do in a mechanism problem is almost as important as knowing what *to* do. So here's a list of do's and don'ts for writing mechanisms.

- **Don't confuse mechanism problems with multistep synthesis problems.** This is a common mistake. Mechanism problems give you all of the reagents that you need to convert the starting material into the product. So, don't supply additional reagents on your own.

- **Do use all of the reagents given in a mechanism problem.** Mechanism problems don't include any extraneous reagents that are not used in a mechanism, so your reaction mechanism must account for the use of all of the reagents.
- **Don't confuse solvents and base scavengers with reagents.** Be able to recognize typical solvents that will generally not come into play in a mechanism — solvents such as THF, DMF, DMSO, $CHCl_3$, CH_2Cl_2, and so on. If you recognize these solvents, you won't try to incorporate the solvent into the mechanism (although it's sometimes acceptable to use the solvent for proton transfers, particularly alcohol solvents and water). Also, base scavengers (like pyridine and triethylamine) are sometimes added to neutralize any acid formed in the reaction, but often don't have much bearing on the mechanism itself.
- **Do get in the habit of drawing out all the atoms at the reaction centers.** Drawing out full Lewis structures rather than line-bond structures for at least the portions of the molecule that change makes losing or misplacing atoms or charges less likely. Drawing out atoms becomes particularly important when charges are involved in a mechanism, because spotting which atoms have charge is much easier when all of the atoms are explicitly drawn out.
- **Don't try to do two things at once in a mechanism.** Take the mechanism one step at a time. That's not to say that there won't be more than one arrow in a given step (there often will be), but don't try to do two *steps* at once. Don't protonate an alcohol and kick off water to make a carbocation in the same step, for example. Make these separate steps.
- **Do draw out all resonance structures for intermediates.** Although drawing the resonance structures of reactive intermediates may not be required by your professor, doing so is good practice. For example, when writing the mechanism for the electrophilic aromatic substitution reaction (see Chapter 13), draw out all of the resonance structures for the cationic intermediate.
- **Do look where you're going.** If you want to go from Tennessee to Utah, you don't just get in your car, drive in any direction, and hope you'll eventually get there. In other words, even though a step you've proposed looks like it could conceivably happen, make sure that step will get you headed in the right direction toward the product. Ask yourself what bonds must be broken and what bonds must be formed in order to take the starting material into the product. Keep the answers to these questions in the back of your mind while you work the mechanism so you can keep track of where you're going.
- **Don't overanalyze why you wouldn't get a different product than the one indicated.** You're given the product, so you don't need to worry too much about why the indicated product is formed rather than another. Often minor products in a reaction are shown to be the product because

the professor wants you to figure out how the reaction made these minor products. Asking questions of why things happen is a sign of an excellent student, but getting too bogged down on why you form one product over another in a shown mechanism may not yield much. As a general principle, draw the mechanism first, and ask questions later.

- **Do ignore spectator ions.** You often see ionic reagents that include potassium (K), sodium (Na), or lithium (Li) as parts of the reagent. It's often a good idea to cross off these spectator ions so you don't get tempted to include them in the mechanism. For example, if the reagent is NaOH, cross off the sodium and make the reagent OH^-. That way you won't be tempted to include the sodium (Na) cation in the mechanism.
- **Do ask yourself if all of your proposed steps and intermediates are reasonable.** Do you always show minuses attacking plusses (and never, ever, vice-versa)? If you're in acidic conditions, did you make sure that you didn't form any negatively charged intermediates? If you're under basic conditions, did you make sure that you didn't form any positively charged intermediates? Did you make sure to never draw a pentavalent carbon (a carbon with five bonds) or break any of the rules of valence? Do all of the charges balance? Ask yourself these kinds of questions after you propose a mechanism.
- **Do be able to work the different types of mechanisms (discussed in the following section).** After working many problems, you'll spot mechanism patterns and you'll begin to notice that some mechanisms are similar to each other.

Types of Mechanisms

After working many problems, you notice that patterns in working mechanisms emerge for different kinds of reaction mechanisms. These most common different kinds of mechanisms are shown in the following list. Of course, some of these kinds of mechanism overlap each other. For example, often in acid mechanisms you make cations, and often in base mechanisms, you generate anions. Determining the kind of mechanism the reaction you're drawing the mechanism for can help you organize your thoughts when tackling problems.

- **Thermal mechanisms:** These are mechanisms with no reagents. These mechanisms are seen mostly in the second semester of organic chemistry, but the Diels-Alder reaction is an example of this mechanism (see Chapter 12).
- **Nucleophile-electrophile mechanisms:** These are probably the most common types of mechanisms. If you can do nucleophile-electrophile

mechanisms, you have understood a big part of organic chemistry. These mechanisms involve *nucleophiles* (nucleus lovers) attacking *electrophiles* (electron lovers). Typically, some species with a lone pair of electrons (a nucleophile) attacks an electron deficient carbon (an electrophile).

- **Acid-base mechanisms:** These mechanisms are identifiable by seeing a strong acid (like HCl or H_2SO_4) or a strong base (like $NaNH_2$) as the reagent. With acid mechanisms, you typically don't want to form any species that have net negative charges (with the exception of an acid's conjugate base which is usually negatively charged), and with base mechanisms, you don't want to form any species that have net positive charges. Typically, the first step in acid mechanisms is protonation, while in a base mechanism the first step is deprotonation.
- **Carbocation mechanisms:** These mechanisms take place generally under acidic conditions. (You won't see net positive charges — like the positive charge on a carbocation — under basic conditions.) Watch out for carbocation rearrangements in these mechanisms (like alkyl or hydrogen shifts). If an intermediate has a net negative charge, you probably did something wrong (you're probably missing a proton transfer step).
- **Anion mechanisms:** These mechanisms are found mostly in carbonyl reactions (ketones, aldehydes, and so on), and they usually take place under basic conditions. You don't see these reactions very often in the first semester of organic chemistry.
- **Free-radical mechanisms:** These are somewhat less common than the other types of mechanism, but they do pop up occasionally. When you see light (hv), or peroxide (ROOR) think free-radical mechanisms. You see radical mechanisms in the bromination of alkanes using light and bromine, for example (Chapter 7). When working free-radical mechanisms, use single-headed arrows rather than double-headed arrows to show the movement of only one electron. Drawing out all initiation, propagation, and termination steps is standard practice for many free-radical reactions.

dif-

Seeing by Example: Example Mechanism Problem

I now apply these principles to an example. Suppose you're asked to propose a mechanism for the conversion of the alcohol shown in Figure B-1 to the alkene shown in the same figure.

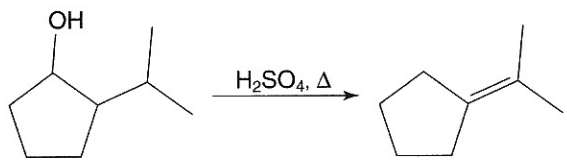


Figure B-1: An example mechanism problem.

First, you want to identify what kind of mechanism you're dealing with. Is it an acid or a base mechanism? Is it a nucleophile or electrophile mechanism? Is it a free radical mechanism? Because the reagent is sulfuric acid (H_2SO_4) plus Δ (a symbol that indicates that the reaction mixture is heated), the reaction will be an acid reaction.

Second, identify where you're going in the mechanism. Converting an alcohol into an alkene usually involves dehydration (loss of water). But you may notice that the alkene in the product is in an unusual position, because dehydration usually puts the alkene adjacent to the starting alcohol. The product in this case has the double bond one carbon atom further away from its expected position. So, you might expect something unusual in this mechanism that accounts for the unusual regiochemistry of the reaction.

Now that you know approximately where you're going in this mechanism, you can begin to propose a route to get there. In an acid mechanism, the first thing you want to look for is a site on the molecule that can be protonated. The only basic site on the starting material in this case is the alcohol, so the first step would be protonation of the alcohol group by sulfuric acid.



The first step in acid mechanisms is almost always protonation.

As always, follow the conventions for arrow pushing (detailed in Chapter 3), drawing double-headed arrows from electrons to where they're going. (The only mechanisms that use single-headed arrows are free-radical mechanisms.)

Because many professors of organic chemistry are convinced that the innermost circle of Dante's hell is reserved for those students who consistently draw protonation incorrectly, make sure to always draw the arrow from the electrons on the base to the acidic proton that the electrons are attacking. Never commit the unpardonable sin of drawing an arrow from an acid H^+. Also, to make following the movement of atoms and charges easier, the atoms on the parts of the molecule that change in the reaction are drawn out explicitly with the full Lewis structure, as shown in Figure B-2.

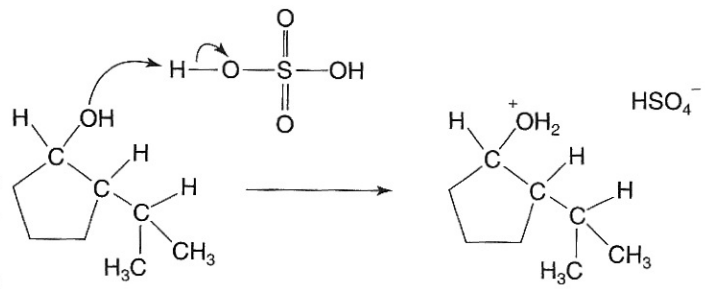


Figure B-2: First step.

Next, examine the consequences of the protonation. What can you do now that you couldn't before? One thing you can do now that the alcohol is protonated is to form a carbocation. While hydroxide ion, OH^-, is a bad leaving group (recall that strong bases are bad leaving groups), water is a good leaving group. Therefore, as in a typical alcohol dehydration mechanism (Chapter 9), the next step involves the loss of water to create a secondary carbocation, as shown in Figure B-3.

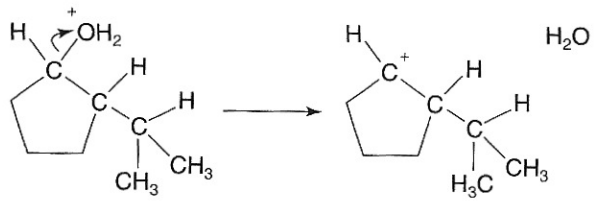


Figure B-3: Making a carbocation.

In alcohol dehydration, when the carbocation is formed, the next step is usually the formation of the double bond by eliminating a proton. Doing so at this step, however, would form the double bond in the wrong position. Somehow, the carbocation needs to move so that when hydrogen is eliminated the double bond is formed in the correct position.

On closer inspection, you may notice that the carbocation is located next to a tertiary carbon center. The carbocation is currently a secondary carbocation, but badly wants to become a tertiary carbocation. (Recall that tertiary carbocations are more stable than secondary carbocation.) A more pragmatic thought process might be that this is where the cation *must* move to in order to get elimination in the correct place. To get the carbocation into the tertiary position, you perform a hydride shift, which moves the tertiary hydrogen atom and both of the electrons in the C–H bond to the cation center, leaving the tertiary carbon with the positive charge. This step is shown in Figure B-4.

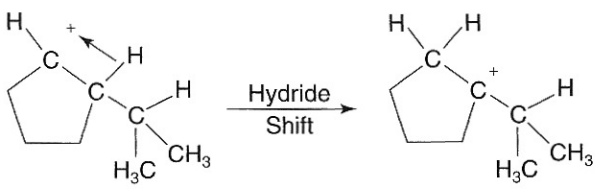


Figure B-4: Watch out for shifts in cation mechanisms.

Now, the elimination of a proton leads to the correct alkene. I show the deprotonation in Figure B-5, using water to regenerate a molecule of acid. You could also use the conjugate base of sulfuric acid as the base here.

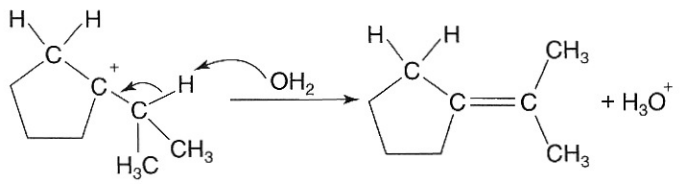


Figure B-5: Forming the alkene.

Appendix C

Glossary

achiral: A molecule that's superimposable on its mirror image. Achiral molecules do not rotate plane-polarized light.

acid: A proton donor or an electron pair acceptor.

alcohol: A molecule containing a hydroxyl (OH) group. Also a functional group.

aldehyde: A molecule containing a terminal carbonyl (CHO) group. Also a functional group.

alkane: A molecule containing only C-H and C-C single bonds.

alkene: A molecule containing one or more carbon-carbon double bonds. Also a functional group.

alkyne: A molecule containing one or more carbon-carbon triple bonds. Also a functional group.

allylic carbon: An sp^3 carbon adjacent to a double bond.

amide: A molecule containing a carbonyl group attached to a nitrogen ($-CONR_2$). Also a functional group.

amine: A molecule containing an isolated nitrogen (NR_3). Also a functional group.

anion: A negatively charged atom or molecule.

anti addition: A reaction in which the two groups of a reagent X-Y add on opposite faces of a carbon-carbon bond.

anti conformation: A type of staggered conformation in which the two big groups are opposite of each other in a Newman projection. See Figure C-1.

anti-aromatic: A highly unstable planar ring system with $4n\pi$ electrons.

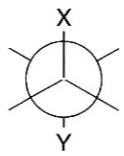


Figure C-1: Newman projection of an anti conformation.

anti-periplanar (a.k.a. anticoplanar): The conformation in which a hydrogen and a leaving group are in the same plane and on opposite sides of a carbon-carbon single bond. The conformation required for E2 elimination.

aprotic solvents: Solvents that do not contain O-H or N-H bonds.

aromatic: A planar ring system that contains uninterrupted p orbitals around the ring and a total of $4n + 2\pi$ electrons. Aromatic compounds are unusually stable compounds.

aryl: An aromatic group as a substituent.

axial bond: A bond perpendicular to the equator of the ring (up or down) in a chair cyclohexane. See Figure C-2.

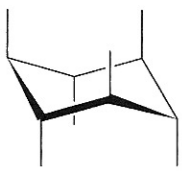


Figure C-2: Axial bonds.

base: A proton acceptor or an electron pair donor.

benzyl group: A benzene ring plus a methylene (CH_2) unit (C_6H_5—CH_2).

benzylic position: The position of a carbon attached to a benzene ring.

benzyne: A highly reactive intermediate. A benzene ring with a triple bond. See Figure C-3.



Figure C-3: Benzyne.

bicyclic: A molecule with two rings that share at least two carbons.

Brønsted acid: A proton donor.

Brønsted base: A proton acceptor.

carbanion: A negatively charged carbon atom.

carbene: A reactive intermediate, characterized by a neutral, electron-deficient carbon center with two substituents (R_2C:).

carbocation: A positively charged carbon.

carbonyl group: A carbon double bonded to oxygen (C=O).

carboxylic acid: A molecule containing a carboxyl (COOH) group. Also a functional group.

cation: A positively charged molecule or atom.

chair conformation: Typically, the most stable cyclohexane conformation. Looks like a chair. See Figure C-4.

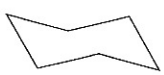


Figure C-4: Chair.

chemical shift: The location of an NMR peak relative to the standard tetramethylsilane (TMS), given in units of parts per million (ppm).

chiral center: A carbon or other atom with four nonidentical substituents.

chiral molecule: A molecule that's not superimposable on its mirror image. Chiral molecules rotate plane-polarized light.

cis: Two identical substituents on the same side of a double bond or ring.

configuration: The three-dimensional orientation of atoms around a chiral center. It's given the designation R or S.

conformation: The instantaneous spatial arrangements of atoms. Conformations can change by rotation around single bonds.

conjugate acid: The acid that results from protonation of a base.

conjugate base: The base that results from the deprotonation of an acid.

conjugated double bonds: Double bonds separated by one carbon-carbon single bond. Alternating double bonds.

constitutional isomers: Molecules with the same molecular formula but with atoms attached in different ways.

coupling constant: The distance between two neighboring lines in an NMR peak (given in units of Hz).

coupling protons: Protons that interact with each other and split the NMR peak into a certain number of lines following the $n + 1$ rule.

covalent bond: Bond in which the two electrons are shared between the two atoms.

dehydrohalogenation: Loss of a hydrohalic acid (like HBr, HCl, and so on) to form a double bond.

delta value (a.k.a. δ value): The chemical shift. The location of an NMR peak relative to the standard tetramethylsilane (TMS), given in units of parts per million (ppm).

diastereomers: Stereoisomers that are not mirror images of each other.

Diels-Alder reaction: A reaction that brings together a diene and a dienophile to form bicyclic molecules and rings.

diene: A molecule that contains two alternating double bonds. A reactant in the Diels-Alder reaction.

dienophile: A reactant in the Diels-Alder reaction that contains a double bond. Dienophiles are often substituted with electron-withdrawing groups.

dipole moment: A measure of the separation of charge in a bond or molecule.

doublet: Describes an NMR signal split into two peaks.

eclipsed conformation: Conformation about a carbon-carbon single bond in which all of the bonds off of two adjacent carbons are aligned with each other (0° apart when viewed in a Newman projection). See Figure C-5.

Figure C-5: Newman projection of eclipsed conformation.



E isomer: Stereoisomer in which the two highest priority groups are on opposite sides of a ring or double bond.

E1 elimination reaction: A reaction that eliminates a hydrohalic acid (like HCl, HBr, etc) to form an alkene. A first order reaction that goes through a carbocation mechanism.

E2 elimination reaction: A reaction that eliminates a hydrohalic acid (like HCl, HBr, etc) to form an alkene. A second order reaction that occurs in single step, in which the double bond is formed as the hydrohalic acid is eliminated.

electronegativity: A term describing the electron piggishness of an atom. More technically, a measure of the tendency of an atom to attract the electrons in a covalent bond to itself.

electrophile: Electron lover. A molecule that can accept a lone pair of electrons (a Lewis acid).

enantiomers: Molecules that are nonsuperimposable mirror images of each other.

equatorial: The bonds in a chair cyclohexane that are oriented along the equator of the ring. See Figure C-6.

Figure C-6: Equatorial.



ester: A molecule containing a carbonyl group adjacent to an oxygen. Also a functional group.

ether: A molecule containing oxygen singly bonded to two carbon atoms. Also a functional group. Ether often refers to diethyl ether.

fingerprint region: Region of an IR spectrum below 1,500 cm^{-1}. The fingerprint region of the IR spectrum is often complex and difficult to interpret.

functional group: A reactivity center.

gauche conformation: A type of staggered conformation in which two big groups are next to each other (shown in a Newman projection in Figure C-7).

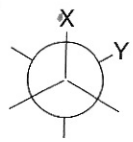


Figure C-7: Newman projection of a gauche conformation.

halide: A member of the VIIA column of the Periodic Table (like F, Cl, Br, I, and so on). Or a molecule that contains one of these atoms. Also a functional group.

Hückel's rule: A rule that states that completely conjugated planar rings with $4n + 2\pi$ electrons are aromatic.

hybrid orbitals: Orbitals formed from mixing together atomic orbitals, like the sp^x orbitals, which result from mixing *s* and *p* orbitals.

hyperconjugation: Weak interaction (electron donation) between sigma bonds with *p* orbitals. Hyperconjugation explains why alkyl substituents stabilize carbocations.

inductive effects: Electron donation or withdrawal by electropositive or electronegative atoms through the sigma bond framework.

intermediate: Any species formed in a reaction on the way to making the product. Typically, intermediates are unstable.

ionic bond: Bond in which the electrons are unshared between two atoms.

IR spectroscopy: An instrumental technique that measures IR light absorption by molecules. Can be used to determine functional groups in an unknown molecule.

isolated double bonds: Double bonds separated by more than one carbon-carbon single bond.

J value: The coupling constant between two peaks in an NMR signal. Given in units of Hz.

ketone: A compound that contains a carbonyl group attached to two carbons. Also a functional group.

kinetic product: The product that forms the fastest. (This product has the lowest energy of activation.)

kinetics: The study of reaction rates.

Lewis acid: An electron pair acceptor.

Lewis base: An electron pair donor.

Markovnikov's rule: A rule that states that electrophiles add to the less highly substituted carbon of a carbon-carbon double bond (or the carbon with the most hydrogen atoms).

mass spectrometry: An instrumental technique involving the ionization of molecules into fragments. Can be used to determine the molecular weights of unknown molecules.

meso: Molecules that have chiral centers but are achiral as a result of one or more planes of symmetry in the molecule.

meta: Describes the positions of two substituents on a benzene ring that are separated by one carbon. See Figure C-8.

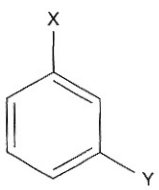


Figure C-8: Meta.

meta-directing substituent: Any substituent on an aromatic ring that directs incoming electrophiles to the meta position.

molecular ion: The fragment in a mass spectrum that corresponds to the cation radical ($M^{+\cdot}$) of the molecule. The molecular ion gives the molecular mass of the molecule.

molecular orbital theory: Model for depicting the location of electrons that allows electrons to delocalize across the entire molecule. A more accurate but less user-friendly theory than the valence-bond model.

multistep synthesis: Synthesis of a compound that takes several steps to achieve.

***n* + 1 rule:** Rule for predicting the coupling for a proton in ^{1}H NMR spectroscopy. An NMR signal will split into $n + 1$ peaks, where n is the number of equivalent adjacent protons.

natural product: A compound produced by a living organism.

nitrile: A compound contain a cyano group: a carbon triply bonded to a nitrogen (CN). Also a functional group.

NMR: Nuclear magnetic resonance sprectroscopy. A technique that measures radio frequency light absorption by molecules. A powerful structure-determining method.

node: A region in an orbital with zero electron density.

nucleophile: Nucleus lover. A molecule with the ability to donate a lone pair of electrons (a Lewis base).

nucleophilicity: A measure of the reactivity of a nucleophile in a nucleophilic substitution reaction.

optically active: Rotates plane-polarized light.

orbital: The region of space in which an electron is confined (the electron "apartment").

organic compound: Carbon-containing compound.

ortho: Describes the positions of two substituents on a benzene ring that are on adjacent carbons. See Figure C-9.

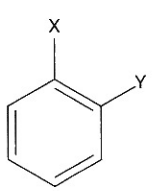


Figure C-9: Ortho.

ortho-para director: An aromatic substituent that directs incoming electrophiles to the ortho or para positions.

oxidation: A reaction that involves the loss of electrons by an atom or molecule.

para: Describes the positions of two substituents on a benzene ring that are separated by two carbons. See Figure C-10.

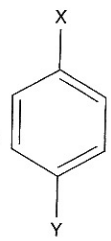


Figure C-10: Para.

phenyl ring: A benzene ring as a substituent.

pi bond (a.k.a. π bond): A bond with electron density above and below the two atoms, but not directly between the two atoms. Found in double and triple bonds.

pKa: The scale for defining a molecule's acidity (pKa = –log Ka).

plane-polarized light: Light that oscillates in a single plane.

plane of symmetry: A plane cutting through a molecule in which both halves are mirror images of each other.

protic solvent: A solvent that contains O-H or N-H bonds.

proton: An H^+ ion. Also a positively charged nuclear particle.

R group: Abbreviation given to an unimportant part of a molecule. Indicates the *R*est of molecule.

Racemic mixture: A 50:50 mixture of two enantiomers. Racemic mixtures are optically inactive (don't rotate plane-polarized light).

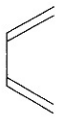
radical: An atom or molecule with an unpaired electron.

reduction: A reaction involving the gain of electrons by an atom or molecule.

resonance structures: Structures used to better depict the location of pi and nonbonding electrons on a molecule. A molecule looks like a hybrid of all resonance structures.

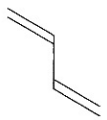
s-cis conformation: A conformation in which the two double bonds of a conjugated diene are on the same side of the carbon-carbon single bond that connects them. The required conformation for the Diels-Alder reaction. See Figure C-11.

Figure C-11: s-cis conformation.



s-trans conformation: The conformation in which the two double bonds of a conjugated diene are on opposite sides of the carbon-carbon single bond that connects them. See Figure C-12.

Figure C-12: s-trans conformation.



sigma bond (a.k.a. σ bond): A bond in which electrons are located between the nuclei of the bonding atoms. Single bonds are sigma bonds.

singlet: Describes an NMR signal consisting of only one peak.

S_N1 reaction: A first order substitution reaction that goes through a carbocation intermediate.

S_N2 reaction: A second order substitution reaction that takes place in one step and has no intermediates.

***sp*:** A hybrid orbital made by mixing one *s* orbital and one *p* orbital.

***sp*^{2}:** A hybrid orbital made by mixing one *s* orbital and two *p* orbitals.

***sp*^{3}:** A hybrid orbital made by mixing one *s* orbital and three *p* orbitals.

staggered conformation: Conformation about a carbon-carbon single bond in which bonds off of one carbon are at a maximum distance apart from bonds coming off of an adjacent carbon (60° apart when viewed in a Newman projection). See Figure C-13.



Figure C-13: Newman projection of a staggered conformation.

stereochemistry: Study of molecules in three dimensions.

stereoisomers: Molecules that have the same atom connectivity, but different orientations of those atoms in three-dimensional space.

steric hindrance: Term referring to the way that atoms can shield a site by getting in the way of approach of a reactant.

substituent: A piece that sticks off of the main carbon chain or ring.

syn addition: A reaction in which two groups of a reagent X-Y add on the same face of a carbon-carbon double bond.

tautomers: Molecules that differ in the placement of a hydrogen and double bonds and are easily interconvertible. Keto and enol forms are tautomers.

thermodynamic product: The reaction product with the lowest energy.

thermodynamics: Study of the energies of molecules.

thiol: A molecule containing an SH group. Also a functional group.

transition state: The highest point on the energy hill that takes one species into another.

triplet: Describes an NMR signal split into three peaks.

Z isomer: Isomer in which the two highest-priority substituents are on the same side of a double bond or ring.

Index

• Numbers •

1*s* orbital, shape, 22
2*s* orbital, shape, 22
3D
 chiral center, 96–97
 constitutional isomers, 94–95
 diastereomers, 104–105
 enantiomers, 95–96
 Fischer projections, 105–108
 introduction, 93
 molecule drawings, 94
 plane-polarized light, 103–104
 stereoisomers, 94–95
 symmetry, 101–103

• A •

acetone, 87
acetylide chemistry, alkynes, 172–173
achiral molecules, 95, 108, 361
acid, 361
acid base chemistry
 arrhenius acids, 66–67
 introduction, 65
 pKa scale, 65
acid-base mechanisms, 357
acidity
 aromatic compounds, 228–229
 comparing, 228–229
acids
 Brønsted-Lowry definition, 67
 comparing acidities of organic molecules, 69–73
 conjugate acids, 67
 conjugate bases, 70
 electrophiles (Lewis acids), 68
 Lewis acids, 68–69
 values, pKa scale, 73–74
activation energy, 181–182
acylation, Friedel-Crafts, 235
alcohols
 alpha cleavage, 259
 C-H absorptions, 276
 carbonyl compounds, 198–199
 classifying, 195–196
 definition, 361
 dehydration, 201–202
 dehydration, alkene formation, 154
 Diels-Alder reaction, 210
 ethanol, 84
 ethers, 202
 Grignard reaction, 200–201
 naming, 196–197
 oxidation, 202–203
 parent chain, 197
 reactions, 198–201, 201–203
 sugars and, 84
 water across double bonds, 198
 water loss, mass spectrometry, 260–261
 Williamson ether synthesis, 202
aldehydes, 86–87, 361
alkanes
 branching alkanes, 115–118
 bromination, 139
 cycloalkanes, 130–134
 definition, 361
 free radical halogenation, 136–139
 functional groups, 77
 hydrogens, saturated, 143–146
 nomenclature, 113–120
 smashing, mass spectrometry, 259
 straight-chain, 114
 substituent naming, 119–120
alkenes
 bromination, 164
 C-H absorptions, 277
 carbenes, 166–167
 carbocation, 156–157, 157–161
 cis stereoisomers, 149
 commerical uses, 79
 common names, 148
 compounds from, 143
 conjugated (*See* conjugated alkenes)
 coupling, 154–155
 cyclopropane rings, 166–167
 definition, 142–143, 361
 dihydroxylation, 163–164
 double bonds, hydration, 161–164
 double bonds, multiple, 148
 epoxides, 167

alkenes *(continued)*
formation, 153–155
halides, 157
hydroboration, 162–163
hydrogenation, 168
hydrohalic acids, 156–157
multiple bonds, 151
nomenclature, 146–148
nomenclature, E/Z system, 150–151
ozonolysis, 165
parent chain, numbering, 146–147
permanganate oxidation, 165–166
R groups, 78
reactions, 156–168
rings, 79
stabilities, 152–153
stereochemistry, 149–151
steric repulsion, 153
substituents, 151
substitution, 152
trans stereoisomers, 149
Wittig reaction, 154–155
alkylated benzenes, oxidation, 236
alkynes
acetylide chemistry, 172–173
bond angles, 81
brominating, 173–174
C-H absorptions, 277
common names, 170
definition, 361
dehydrohalogenation, 172
forming, 171–176
hydroboration, 176
hydrogenation, 174–175
internal, 172
nomenclature, 169–170
orbitals, 170–171
oxymercuration, 175–176
R groups, 80
rings, 171
terminal, 172
allylic carbon, 361
alpha cleavage, mass spectrometry, 259–261
amides, 90, 361
amines
alpha cleavage, 260
C-H absorptions, 276
definition, 361
Diels-Alder reaction, 210
introduction, 91
-ane suffix, 146
anion mechanisms, 357
anions, 20, 361
answer checking, five commandments of multisynthesis, 351
anti addition, 361
anti-aromatic, 361
anti-aromatic rings, 218
anti conformation, 361
anti conformers, butane, 129
anti-periplanar, 362
anti-periplanar geometry, 192
antibonding molecular orbitals, 220
anticoplanar, 362
antifeedants in plants
caterpillars and, 12
organic molecules and, 12
aprotic solvents, 362
aromatic compounds
acidities, 228–229
basicities, 229–230
characteristics, 218
common, 232
diversity of, 217–218
heteroatoms, 217
Hückel, Erich and, 218–219
Hückel number, 225
naming, 230–232
nucleophilic aromatic substitution, 243–245
overview, 216–219
planar molecules, 225
reactions and, 216
regions, benzenes, 312
rings, 225
aromatic substituents, 241
aromaticity
determining, 225–228
molecular orbital theory, 219–225
pi electrons, 227
rings, magnetic field, 289
aromatics, 362
aromatics (arenes)
benzene, 215
C-H absorptions, 277
Kekulé and, 215
rings, 81
Arrhenius acids
dissociation, 66
hydromium ions and, 66
hydroxide ions and, 66
arrow pushing, 51
arrows
double-headed arrow, 52
equilibrium arrow, 52
fishhook, 52
reaction arrow, 52

resonance arrow, 52
single-headed arrow, 52
aryls, 362
aspirin
COX enzymes and, 16
willow bark as natural product, 16
atom
hybridization, 71
reaction center, drawing, 355
atomic number, Periodic Table, 20
atomic orbitals, molecular orbitals and, 220
atoms
bonding, 24
comparison, 70–71
covalent bonding, 27
dipole moments, 29
dipole moments, predicting molecule, 31–32
dipole vector, 30
dipoles, 19
electronegativity, 27–29
electronegativity effects, 72
energy shells, 20
hybridizing, predicting, 35–36
lone pairs, structures, 51
orbitals, 19
protons, 20
resonance structures, 54
size, negative charge and, 70
substituents, hybridizing and, 35
VSEPR Theory, 32–36
attitude, success and, 323
Aufbau chart, orbitals and, 23
axial bonds, 362
axial hydrogens, chair conformation and, 132

• B •

bases
conjugate bases, 67
definition, 362
Lewis bases, 68–69
nucleophiles (Lewis bases), 68
basicities, aromatic compounds, 229–230
beer, fermentation and, 330
benzaldehyde, 87
benzene
alkylated, oxidation, 236
carbanions and, 243
carbon atoms, 221
disubstituted, synthesis of, 236–241
electrophilic aromatic substitution, 232–236
fused rings, 217–218
Kekulé, August and, 215
mass spectrometry, 261–262
MO diagram, 221–222
MOs, 222–224
naming benzenes, 230–232
p orbitals, 222
rings, aromatic region and, 312
structure, 216–217
substituted, 231
substituted, synthesis, 241–242
benzopyrene, fused rings, 217
benzyl group
benzenes, 230
definition, 362
benzylic position, 362
benzyne, 362
$Be(OH)_2$ (beryllium hydroxide), dissociation and, 66–65
betaine, 155
bicyclic, 363
bicyclic products, Diels-Alder reaction, 211–212
bioorganic chemists
COX (cyclooxegenase) enzymes, 16
description, 15–16
enzymes, 15
bonding
angles, Alkynes, 81
classifications, 28
covalent bonding, 27
dipole moment prediction, 30
double bonds, 37
homolytic cleavage, 136–137
introduction, 24
ionic, 25–27
orbitals, hybrid, 33–35
pi bonds, 36–39
sigma bonds, 36–39
single bonds, 37
torsional strain, 128
triple bonds, 37
VSEPR Theory, 32–36
bonding molecular orbitals, 220
bonds
Hooke's law, 268–269
infrared absorption, 268–271
vibration, IR light absorption and, 269–270
branching alkanes
chain length, 115
chain numbering, 116
isomers, 115
substituents, 116–118

bromination
 alkenes, 164
 alkynes, 173–174
 selectivity of, 139
bromine, isotopes, 256
Brønsted acid, 363
Brønsted base, 363
Brønsted-Lowry definition of acids and bases, 67
Buckyballs, 332–333
butane, structure, 114
butane
 chlorination, 138
 conformations, 128–130

• C •

C-H absorptions, IR spectroscopy
 alcohols, 276
 alkenes, 277
 alkynes, 277
 amines, 276
 aromatics, 277
 carbonyl groups, 276
calicheamicin molecules, 80
carbanion
 benzenes and, 243
 definition, 363
carbenes
 alkenes, 166–167
 definition, 363
carbocation
 alkenes, 156–157, 157–161
 definition, 363
 hyperconjugation, 158
 mechanisms, 357
 rearrangements, 159–161
 resonance stabilization, 159
carbon
 benzene, 221
 carbon-carbon bonds, 17
 carbon-metal bonds, 17
 electron configuration, 24
 line-bond structures, 47
 multistep synthesis and, 348–349
 organic molecules and, 14
carbon NMR, 296–298
carbonyl compounds
 alcohols and, 198–199
 aldehydes, 86–87
 amides, 90
 amines, 91
 C-H absorptions, 276
 carboxylic acid, 89
 Diels-Alder reaction, 210
 esters, 89
 ketones, 87–88
 nitriles, 91
 nitrogen-containing functional groups, 90
carbonyl group, 363
carboxylic acids, 89, 363
catalytic cracking reaction, alkanes, 136
caterpillars, antifeedants and, 12
cations
 definition, 363
 description, 20
 resonance structures and, 57
chain reactions, 137
chair conformation
 axial hydrogens and, 132
 cyclohexane, 131
 definition, 363
 diaxial strain, 133–134
 drawing, 132–134
 ring flip, 133
 stable, drawing, 134–135
chemical equivalency, NMR, 286–287
chemical reactions, organometallic chemists and, 17
chemical shifts, 363
chemical shifts, NMR
 diamagnetic anisotropy, 288
 fragment combining, 308
 introduction, 285–286
 molecular structures and, 319
chemists
 Corey, E.J., 339–340
 Fischer, Emil, 340–341
 Hodgkin, Dorothy, 340
 Kekulé, August, 338
 Kolbe, Adolf, 342
 Nicolaou, K.C., 338–339
 Pasteur, Louis, 340
 Pauling, Linus, 341
 Pople, John, 341
 Wöhler, Friedrich, 342
 Woodward, Robert Burns, 337–338
chiloglottone, 88
chiral center
 definition, 108, 363
 diastereomers, 104–105
 introduction, 96
 R/S nomenclature, 97–98
 thumb technique, 101

chiral molecules
definition, 108, 363
introduction, 95
plane-polarized light, 103–104
chlorination
of butane, 138
of methane, 136
selectivity of, 139
chlorine, molecules, isotopes and, 256
cis, 363
cis isomer, stability, 152–153
cis stereoisomer
alkenes, 149
description, 131
class attendance, success and, 326
CN (cyano groups), Diels-Alder reaction, 210
complete dissociation, acids, 66
compounds
from alkenes, 143
computational chemists and, 17
natural products, 16
natural products chemists and, 16
computational chemists
description, 17–18
relational drug design and, 18
in silico drug design and, 17
condensed structures, 46–47
configuration, 363
conformations
anti conformers, 129
butane, 128–130
cyclohexame, 131–134
definition, 363
eclipsed, 128, 129
gauche interactions and, 129
Newman projections and, 127–128
staggered, 128
straight-chain alkanes, 126–130
conjugate acids, 67, 364
conjugate addition
kinetics and thermodynamics, 209
reaction diagrams, 207–208
conjugate bases
acids and, 70
definition, 364
introduction, 67
conjugated alkenes
Diels-Alder reaction, 209–212
hydrohalic acids and, 206–209
conjugated double bonds
definition, 364
introduction, 205–206
constitutional isomers
definition, 364
stereoisomers and, 94–95
core electrons, 25
Corey, E.J., background, 339–340
coupling
alkenes, 154–155
constants, 293, 299
integration comparison, 320
$n + 1$ rule, 292–293
NMR, 291–292, 298
NMR, ethanol, 292
NMR, tree diagram, 295–296
NMR mistakes, 319–320
non-equivalent hydrogens, 293–295
singlets, 293
coupling constants, 364
coupling protons, 364
covalent bonding
definition, 364
electronegativity and, 27–28
organic compounds, 29
COX (cyclooxegenase) enzymes
aspirin and, 16
bioorganic chemists and, 16
Curl, Robert, 332–333
cycloalkanes
introduction, 130
stereochemistry, 131
cyclobutadiene, MO diagram, 224–225
cyclodecapentaene, aromaticity and, 225
cyclohexane, conformations, 131–134
cyclooctatetraene, aromaticity and, 225
cyclopropanes
alkenes, 166–167
Simmons-Smith reaction, 167

• D •

daily practice, success and, 327
decane, structure, 114
degenerate orbitals
introduction, 22
MOs, 221
degree of unsaturation
molecular formulas, 145–146
molecular structure and, 310–311, 316
NMR problem solving, 303
structures and, 144–145
dehydration of alcohols
alkene formation, 154
overview, 201–202

dehydrohalogenation
 alkenes, 153–154
 alkynes, 172
 definition, 364
delta value, 364
deshielded hydrogens, NMR, 285
detector, mass spectrometer
 mass to charge ratio, 253
 overview, 250
deuterium, NMR, 296
deuterons, NMR, 296
diagrams
 3D, 94–109
 chair conformations, 132–134
 dots, valence electrons, 26
 Frost circles, 221
 mistakes in resonance structures, 62–63
 MO diagram of benzene, 221–222
 MO diagram of cylobutadiene, 224–225
 molecular orbital diagrams, 220–221
 reactions, atoms at center, 355
 structures, 41–42, 45–46
 structures, tips for interpreting, 122
diamagnetic anisotropy, 288
diamine, 91
diastereomers, 104–105, 108, 364
diaxial strain, chair conformation, 133–134
Diels-Alder reaction
 alcohols, 210
 amines, 210
 bicyclic products, 211–212
 carbonyl compounds, 210
 conjugated alkenes, 209–212
 cyano groups (CN), 210
 definition, 364
 dienes and dienophiles, 210–211
 discoveries, 331–332
 ethers, 210
 EWG, 210
 nitro groups (NO_2), 210
 products, 212–214
 stereochemistry, 211
dienes
 definition, 364
 Diels-Alder reaction and, 210–211
dienophiles
 definition, 364
 Diels-Alder reaction and, 210–211
dihydroxylation, alkenes, 163–164
diketone, 88
dipole moments
 definition, 364
 introduction, 29
 molecule, predicting, 31–32
 predicting, 30
dipole vector, 30
dipoles, 19
discoveries
 aspartame, 333–334
 Buckyballs, 332–333
 Diels-Alder reaction, 331–332
 dynamite, 329–330
 explosives, 329–330
 fermentation, 330
 handedness of tartaric acid, 331
 penicillin, 334
 soap, 333
 Teflon, 334–335
 urea synthesis, 330–331
dissociation, acids, 66
disubstituted benzenes, synthesis, 236–241
divalence, 44
dodecane, structure, 114
double bonds
 aromatic compounds, 216
 cleavage, 165–166
 conjugated, 205–206
 electronegative atoms, resonance structures, 58
 equivalents, 144
 hydration, 161–164
 hydrohalic acids across, alkenes, 156–157
 identical groups, 150
 introduction, 37
 Lewis structure, 43
 mass spectrometry, 261–262
 multiple, alkenes, 148
 resonance structures, 57
 resonance structures, alternating around ring, 58
double-headed arrow in diagrams, 52
doublets, 364
dynamite, 329–330

• E •

E1 elimination reaction, 193, 365
E2 elimination reaction, 192–193, 365
E isomer, 365
E/Z system of nomenclature, alkenes, 150–151
eclipsed conformations
 definition, 364
 description, 128
 totally eclipsed, 129
EDG (electron-donating groups), 210

EIMS (electron-ionization mass spectrometry), 251–252
electron ionization, mass spectrometer, 251–252
electron shielding, NMR, 284
electron-withdrawing groups, 238–241
electronegativity
 atoms, 27–29
 definition, 365
 effects of, 72
 increases, 70
 polar covalent, 27–28
 purely covalent, 27–28
 resonance structures, 58
electrons
 arrows and, 53
 atoms, protons and, 20
 carbon configuration, 24
 ground state electron configuration, 23–24
 Heisenberg Uncertainty Principle, 21
 Hund's rule, 23–24
 ions, 20
 Lewis structures, 43
 location, 21
 meta directors, 238–241
 MOs and, 220
 octet rule, 25
 orbitals, 21
 orbitals, filling, 23
 ortho-para activators, 238
 pi-withdrawing groups, 241
 quantum mechanics and, 21
 shells compared to orbitals, 21
 spin, 21
 spin, Hund's rule and, 24
 valence electrons, 25
 VSEPR Theory, 32–36
electrophiles
 definition, 365
 Lewis acids, 68
electrophilic aromatic substitution of benzene
 Friedel-Crafts acylation, 235
 Friedel-Crafts alkylation, 233–234
 introduction, 232
 nitro group reduction, 235–236
electrophilic attack, benzenes, 240
elimination reactions
 E2 reaction, 192–193
 substitution and, 193–194
enantiomers
 3D drawing and, 95–96
 definition, 108, 365
endo addition, 211–212
-ene suffix, 146, 169–170
enzymes, bioorganic chemists, 15–16
epoxide
 alkenes and, 167
 definition, 86
equatorial, 365
equatorial hydrogens, chair conformation, 133
equilibrium, reactions, acid-base, 74–75
equilibrium arrow, 52
esters, 89, 365
ethane, structure, 114
ethanol, 84
ethers
 alcohols and, 202
 definition, 365
 Diels-Alder reaction, 210
 introduction, 85–86
EWG (electron-withdrawing groups), Diels-Alder reaction, 210
exams, success and, 328
exo addition, 211–212
explosives, 329–330
external magnetic field, NMR theory and, 281

• F •

falling behind, success and, 324–325
fermentation discovery, 330
fingerprint region, 366
first-order substitution
 rate-determining step, 188
 S_N1 reaction, 187–191
Fischer, Emil, 340–341
Fischer projections
 meso compounds, 108
 R/S nomenclature, 106–107
 rules for, 105–106
 stereoisomers, 107
fishhook arrows, 52
five commandments of multistep synthesis
 answer checking, 351
 carbon skeletons, 348–349
 mechanisms, 347
 multiple problems, 351
 reactions, 348
 retrosynthesis, 349–351
formal charges, Lewis structures, 43–45
formation of alkenes
 dehydration of alcohols, 154
 dehydrohalogenation, 153–154
formation of alkynes, 171–176

formulas
degrees of unsaturation, 145–146
molecular, drawing isomers from, 123–126
fragmentation patterns, mass spectrometry
alkanes, 259
alpha cleavage, 259–260
benzenes, 261–262
double bonds, 261–262
McLafferty Rearrangement, 261
molecular structure, 311–312
peaks and, 258
water loss, alcohols, 260–261
free radical halogenation
bromination, 139
catalytic cracking reaction, 136
chlorination, 139
initiation, 136–137
propagation, 137
free-radical mechanisms, 357
Friedel-Crafts
acylation, 235
alkylation, alkyl substituents, 233–234
Frost circles, ring systems, 221
functional groups
alkenes, 141–168
carbonyl compounds, 86–91
definition, 366
description, 77
heteroatoms, 82–86
hydrocarbons, 78–82
IR absorption, 273
IR absorption, appearance, 274–275
IR spectrum, 303
molecular structure and, 311
waypoints, 143

• G •

gas, inlet, mass spectrometer, 251
gauche conformation, 366
gauche interaction, conformations and, 129
genetic coding, organic molecules and, 12
Grignard reaction, alcohols, 200–201
ground state electron configuration, orbitals and, 23–24

• H •

halides
alkenes, 157
definition, 366
halogens and, 82
insecticides, 83
halogens, degree of unsaturation and, 303
halogens chlorine, isotopes, 256
handedness of tartaric acid, 331
Haworth projections, stereochemistry and, 131
heat mechanisms, 356
Heisenberg Uncertainty Principle, electron location and, 21
heptane structure, 114
heteroatoms
alcohols, 84
aromatic compounds, 217
ethers, 85–86
halides, 82–84
thiols, 85
hexane
IR spectrum, 273–274
structure, 114
Hodgkin, Dorothy, 340
homolytic cleavage, bond dissociation, 136–137
Hooke's law, bond vibration and, 268–269
HRMS (high-resolution mass spectrometers), compound weight, 255
Hückel, Erich, aromatic rings, 218–219
Hückel's rule, 366
Hund's rule, orbitals, 23–24
hybrid orbitals
bonding and, 33–35
definition, 366
naming, 34
hybridizing atoms
atom comparison and, 71
predicting, 35–36
rule for determining, 36
hydration, double bonds and, 161–164
hydroboration
alkenes and, 162–163
alkynes and, 176
hydrocarbons
alkenes, 78–79
alkynes, 80–81
aromatics, 81–82
hydrogen NMR
chemical shift, 288–290
introduction, 281
hydrogenation
alkenes, 168
alkynes, 174–175

hydrogens
 chair conformation, 132
 coupling, non-equivalent, 293–295
 deshielded, NMR and, 285
 double bond equivalent, 144
 index of hydrogen deficiency, 144
 integrations, 305
 line-bond structures, 49–50
 peak ratio, 305–306
 saturated (*See* saturated hydrogens [alkanes])
 shielded, NMR and, 285
hydrohalic acids
 alkenes, 156–157
 conjugated alkenes and, 206–209
hydronium ion, Arrhenius and, 66
hydroxide ions, Arrhenius acids and, 66
hydroxyl (OH) groups, alcohols, 195–196
hyperconjugation
 carbocations, 158
 definition, 366

• I •

in resonance (NMR), 283
in silico drug design, computational chemists and, 17
index of hydrogen deficiency, 144
inductive effects, 366
infrared absorption, bonds, 268–271
initiation step, reactions, 136–137
inlet, mass spectrometer
 gas phase and, 251
 overview, 250
inorganic compounds, ionic bonds, 29
integration, NMR, 298
 baseline noise, 305
 coupling comparison, 320
integration curve, peak ratio and, 304–306
intermediates
 definition, 366
 resonance structures, mechanisms and, 355
internal alkynes, 172
interpreting structures, tips, 122
iodine, isotopes, 256
ionic bonding
 definition, 366
 electronegativity and, 27–28
 inorganic compounds, 29
 sodium and chlorine, 25–27
ionization, smasher, mass spectrometer, 251–252
ions
 anions, 20
 cations, 20
 electrons and, 20
 negatively charged, 20
 protons and, 20
 spectator, mechanisms, 356
IR (infrared) spectrometer
 absorption, functional groups, 273
 absorption, intensity, 270–271
 C-H absorptions, 275–276
 IR inactive vibrations, 271
 molecular structure and, 315–318
 spectrum, hexane, 273–274
 spectrum, light transmittance, 271–272
 spectrum generation, 270
IR (infrared) spectroscopy, 366
 absorption, bonds, 268–271
 IR light, bond vibration and, 269–270
 NMR spectroscopy and, 267
 sensitivity, 255
IR (infrared) spectrum
 functional groups, 303
 structures, NMR and, 308–309
isolated double bonds, 366
isomers
 branching alkanes and, 115
 cis stereoisomer, 131, 149
 drawing from molecular formula, 123–126
 trans stereoisomers, 131
isotopes
 bromine, 256
 definition, 256
 halogens chlorine, 256
 iodine, 256
 nitrogen rule, 258
IUPAC nomenclature, alkenes, 148

• J–K •

J value, 367
jargon, structures and, 41

Kekulé, August, 338
Kekulé structures
 benzene and, 215
 introduction, 45
ketones, 87–88, 367
kinetic product
 conjugate addition, 208
 definition, 367

kinetics
definition, 367
physical organic chemists and, 17
thermodynamics, conjugate addition and, 209
KOH (potassium hydroxide), dissociation and, 66–67
Kolbe, Adolf, 342
Kroto, Harry, 332–333

• L •

leaving group, S_N2 reaction, 186–187
Lewis acids, 68–69, 367
Lewis bases, 68–69, 367
Lewis structures. *See also* Kekulé structures
conversion to line-bond structure, 48–49
description, 43
double bonds, 43
electrons, 43
formal charges, 43–45
single bonds, 43
triple bonds, 43
life, organic molecules and, 13
line-bond structures
conversion from Lew structures, 48–49
hydrogens, 49–50
introduction, 47
lone-pair atoms, structures and, 51
lone-pair electrons, resonance structures, 54, 57

• M •

magnetic movement, NMR theory and, 281
Markovnikov's rule, 367
Markovnikov, Vladimir
hydroboration, 162–163
introduction, 156
oxymercuration-demercuration, 161–162
mass spectrometer
detector, 250
EIMS (electron-ionization mass spectrometry), 251–252
inlet, 250
molecular ion peak, 254
overview, 250–251
radical cation, 251–252
smasher, 250, 251–252
sorter, 250, 252–253
weigher, 252–253
mass spectrometry
alpha cleavage, 259–260
definition, 250, 367
exam sample, 262–264
fragmentation patterns, 258–264
introduction, 249–250
isotopes, 256–258
key ideas, 264–265
sensitivity, 255
mass to charge ratio, mass spectrometer weigher, 253
materials chemists, 18
McLafferty Rearrangement, mass spectrometry, 261
mechanisms
acid-base, 357
anion, 357
base scavengers and reagents, 355
carbocation, 357
example problem, 357–360
free-radical, 357
heat mechanisms, 356
intermediates, resonance structures, 355
multistep synthesis comparison, 354
multitasking, 355
nucleophile-electrophile, 356–357
reaction mechanisms, 353–360
reagents, 355
solvents and reagents, 355
spectator ions, 356
tips for working, 354–356
mercurinium ions, 162
meso, 367
meso compounds
definition, 108
Fischer projections, 108
symmetry and, 101–103
meta, 367
meta-directing substituent, 367
meta directors, electrons, 238–241
metabolism, organic molecules and, 12
methane, structure, 114
methane chlorination, 136
methyl groups
loss, 262
prefixes, 118–119
mixing orbitals, 34
MO (molecular orbital) theory
antibonding molecular orbitals, 220
atomic orbitals and, 220
benzene diagram, 221–222, 222–224
bonding molecular orbitals, 220

cyclobutadiene, 224–225
degenerate orbitals, 221
electrons and, 220
introduction, 219
molecular oribital diagrams, 220–221
overview, 220
rings, Frost circle, 221
valence bond theory and, 220
models, molecules and, 42
molecular formula, molecular structure and, 315–318
molecular ion peak
mass spectrometer and, 252
mass spectrum and, 254
molecular ions, 367
molecular orbital theory, 368
molecular structure
confirmation, 313–314
degrees of unsaturation, 316
fragments, 311–312
function groups, 311
IR and, 315–318
molecular formula and, 315–318
molecular formula and NMR, 310–311
peak ratio, 311
molecules
3D drawings, 94
achiral, 95
aromatic, characteristics, 218
chiral, 95
dipole moment prediction, 31–32
formulas, drawing isomers from, 123–126
mirror images (enantiomers), 95–96
models and, 42
organometallic chemists, 17
VSEPR Theory, 32–36
monovalence, 44
multistep synthesis
answer checking, 351
carbon skeletons, 348–349
definition, 368
five commandments, 347–351
mechanisms comparison, 354
problem solving tips, 345–351
retrosynthesis, 349–351
synthetic organic chemists and, 15
Vitamin B_{12}, 347

• N •

n + 1 rule
coupling, 292–293
definition, 368
naming
alcohols, 196–197
aromatics, 230–232
benzenes, 230–232
structures, 120–123
natural products
caffeine and, 16
chemists, 16
definition, 368
nicotine and, 16
peyote and, 16
willow bark and, 16
Newman projections
butane conformations, 128–130
conformational analysis and, 127–128
Nicolaou, K.C., 338–339
nitriles, 91, 368
nitro groups, electrophilic aromatic substitution of benzene, 235–236
nitrogen, degree of unsaturation and, 303
nitrogen-containing functional groups, 90
nitrogen rule, isotopes, 258
nitroglycerin, 329–330
NMR (Nuclear Magnetic Resonance) spectroscopy
carbon NMR, 296–298
chemical equivalency, 286–287
chemical shift, 288–290, 299
chemical shifts, standardizing, 285–286
coupling, 291–296
coupling, *n* + 1 rule, 292–293
coupling, singlets, 293
coupling constants, 293, 299
coupling tree diagram, 295–296
definition, 368
deshielded hydrogens, 285
deuterium, 296
deuterons, 296
electron shielding, 284
exchange, 296
external magnetic field, 281
hydrogen NMR, 281
integration, 290–291, 299
introduction, 279
IR spectrum functional groups, 303
magnetic movement and, 281
molecular structure and, 310–311
MRI (magnetic resonance imaging) and, 299
NMR active nuclei, 281
NMR inactive nuclei, 281
overview, 281–284
peak intensity, 290
peak ratio, integration curve and, 304–306
peaks, fragmenting, 306–307

NMR (nuclear magnetic resonance) spectroscopy *(continued)*
problem solving mistakes, 318–320
problems, clues, 302–309
radio waves, 283
reasons for, 280
in resonance, 283
sensitivity, 255
shielded hydrogens, 285
spectrum, 284–287
spin and, 281
spin flipping, 283
structures, IR spectrum and, 308–309
symmetry, 286–287
TMS (tetramethylsilane) and, 285–286
NO_2 (nitro groups), Diels-Alder reaction, 210
noble gases, 24
node, 368
nonane, structure, 114
note cards for reactions, drawing, 142
nucleophile-electrophile mechanisms, 356–357
nucleophiles
benzenes, 240
definition, 368
Lewis bases, 68
protic solvents and, 186
reactions, 194
roles, 183–184
steric hindrance and, 184
nucleophilic aromatic substitution, 243–245
nucleophilicity, 184, 368
numbering parent chain, alkenes, 146–147
numbers, orbital types and, 22

• O •

octane, structure, 114
octet rule
atom bonding, 25
filled, resonance structures and, 61
resonance structures and, 55
optically active, 109, 368
orbitals. *See also* MO (molecular orbital) theory
1*s*, 22
2*s*, 22
alkynes, 170–171
Aufbau chart, 23
bonding and, 21
carbon electron configuration, 24
definition, 368
degenerate, 22
description, 19
electron spin, 21
electron spin, Hund's rule and, 24
ground state electron configuration, 23–24
Hund's rule, 23–24
hybrid orbitals, 33–35
mixing, 34
numbers in naming, 22
p orbitals, 21
quantum mechanics and, 21
s orbitals, 21
shells and, 21
sp^3 hybridized, 33
syntax, 22
orchid, diketones, 88
organic chemistry
introduction, 11–12
special fields for chemists, 15–18
organic compounds
covalent bonds, 29
definition, 368
natural products chemists and, 16
organic molecules
acidity comparison, 69–73
carbon and, 14
life and, 13
overview, 12
plants, 12
synthetic organic chemists and, 15
vital life force, 14
organometallic chemist, 17
ortho, 368
ortho-para activators, 238
ortho-para directors, 369
oxaphosphetane, 155
oxidation
alcohols, 202–203
definition, 369
oxyanion, 155
oxygen, degree of unsaturation and, 303
oxymercuration, alkynes, 175–176
oxymercuration-demercuration, 161–162
ozonolysis, alkenes, 165

• P •

p orbitals
benzene, 222
shape, 21
pain, COX enzymes and, 16
para, 369
parent chain
alcohols, 197
alkenes, numbering, 146–147

partial dissociation, acids, 66
Pasteur, Louis
 background, 340
 handedness of tartaric acid, 331
Pauling, Linus, 341
peak ratios
 fragmenting, 306–307
 fragments, combining, 308
 integration curve height and, 304–306
 molecular structure, 311
peak splitting, 308
penicillin, 334
pentane, structure, 114
Periodic Table, atomic number, 20
permanganate oxidation, alkenes, 165–166
phenyl group, benzene, 230
phenyl ring, 369
photochemical reaction, 136
photochemistry, physical organic chemists and, 17
physical organic chemists
 kinetics, 17
 photochemistry, 17
 spectroscopy, 17
 termodynamics, 17
pi bond, 369
pi (π) bonds, orbital overlap and, 36–39
pi electrons
 aromaticity and, 227
 resonance structures, 54
pi-withdrawing groups, 241
pKa scale
 acid base chemistry, 65
 definition, 369
 values of common acids, 73–74
plane of symmetry, 369
plane-polarized light
 definition, 369
 introduction, 103–104
 Pasteur, Louis and, 340
plants
 antifeedants, 12
 organic molecules and, 12
polysubstituted benzenes, synthesis, 241–242
Pople, John, 341
prefixes, methyl groups, 118–119
primary carbocations, alkenes, 156
problem working, success tips, 323–324
propagation, reactions, 137
propane, structure, 114
protic solvents
 definition, 369
 nucleophiles and, 186
protons
 atoms, electrons and, 20
 definition, 369
 ions, 20
 number of, 20

• Q–R •

quantum mechanics, electrons and, 21
questions, success and, 327

R group, 369
R/S nomenclature
 chiral centers, 97–98
 configuration, 98–101
 Fischer projections and, 106–107
R-SH groups, 85
racemic mixture
 definition, 369
 introduction, 109
 S_N1 reaction, 190–191
radical cation, mass spectrometry, 251–252
radicals, 369
radio waves, NMR and, 283
rate determining step, 188
rate equation
 S_N1 reaction, 187–189
 S_N2 reaction, 181–182
rational drug design, computational chemists and, 18
reaction arrow, 52
reaction diagrams
 conjugate addition, 207–208
 introduction, 181–182
reaction mechanisms
 reagents, 355
 types, 353–354
reactions
 acid-base, equilibrium, 74–75
 alcohols, 198–201, 201–203
 alkenes, 156–168
 aromatic compounds, 216
 chain reactions, 137
 drawing atoms at center, 355
 multistep synthesis and, 348
 note cards, 142
 nucleophiles, 194
 propagation, 137
 Simmons-Smith, 167
 substitution reactions, 179–180
 substrates, 194
 termination, 137–139
 transition state, 182

reactions *(continued)*
waypoints, 143
Wittig reaction, 154–155
reagents
base scavengers, 355
solvents, 355
rearrangements, carbocation
introduction, 159–161
mass spectrometry and, 261
McLafferty Rearrangement, 261
reduction, 370
resonance arrow, 52
resonance effects, 72–73
resonance stabilization of carbocations, 159
resonance structures
benzene, 216–217
cations, 57
charges on best atoms, 60–61
definition, 370
double bonds, 57
double bonds, alternating around ring, 58
drawing, 56–58
drawing multiple, 59
electronegative atoms, 58
fewest charges, 60
filled octets, 61
importance assignment, 60–61
intermediates, mechanisms and, 355
introduction, 53
lone-pair electrons, 57
mistakes in drawing, 62–63
molecule stabilization and, 72
octet rule, 55
pi electrons, 54
rules, 54–55
triple bonds, 57
retinal, 87
retrosynthesis, 349–351
rings
alkynes, 171
anti-aromatic, 218
Frost circle, 221
fused rings, benzene, 217–218

• S •

s-cis conformation, 370
s orbitals, shape, 21
s-trans conformation, 370
saturated hydrogens (alkanes)
degree of unsaturation, structures, 144–145
introduction, 143–144
molecular formulas, 145–146
second-order substitution, S_N2 mechanism, 180–187
secondary carbocations, alkenes, 156
sensitivity
IR, 255
mass spectrometry, 255
NMR, 255
shells (electrons), orbitals and, 21
shielded hydrogens, NMR, 285
sigma (σ) bonds, 370
Simmons-Smith reaction, cyclopropanes, 167
single bonds
introduction, 37
Lewis structure, 43
single-headed arrow, 52
singlet, 370
singlets, coupling and, 293
size, relating to, 42
Small, Richard, 332–333
smasher, mass spectrometer
alkanes, 259
EIMS (electron-ionization mass spectrometry), 251–252
electron ionization, 251–252
overview, 250
S_N1 reaction
definition, 370
rate equation, 187–189
S_N2 comparison, 191
solvents, 190
stereochemistry, 190–191
substrates, 189
S_N2 mechanism, second-order substitution, 180–187
S_N2 reaction
definition, 370
leaving group, 186–187
S_N1 comparison, 191
solvents and, 185–186
stereochemistry, 185
S_N2 reaction rate, 181–182
S_N2 reactions, substrate and, 182–183
soap discovery, 333
sodium, chlorine bonding, 25–27
sodium borohydride, aldehydes and alcohols, 199
solvents
aprotic, 362
protic, 186
S_N1 reaction, 190
S_N2 reaction and, 185–186
sorter, mass spectrometer
molecular ion peak, 252
overview, 250

sp hybrid orbitals, 370
sp^2 hybrid orbitals, 370
sp^3 hybrid orbitals, 33, 370
specialized areas
 bioorganic chemists, 15–16
 computational chemists, 17–18
 introduction, 14–15
 materials chemists, 18
 natural products chemists, 16
 organometallic chemists, 17
 physical organic chemists, 17
spectator ions, mechanisms and, 356
spectroscopy
 mass spectroscopy, 250
 physical organic chemists and, 17
spin, NMR theory and, 281
spin flipping, NMR, 283
stabilities
 alkenes, 152–153
 resonance stabilization of carbocations, 159
staggered conformations
 definition, 371
 description, 128
 gauche interaction and, 129
stereochemistry
 alkenes, 149–151
 cis stereoisomers, 131
 cycloaklanes, 131
 definition, 371
 Diels-Alder reaction, 211
 Haworth projections, 131
 introduction, 93
 S_N1 reaction, 190–191
 S_N2 reaction and, 185
 terminology, 108–109
 thalidomide and, 109
 trans stereoisomers, 131
stereoisomers
 constitutional isomers and, 94–95
 definition, 371
 Fischer projections and, 107
steric hindrance
 definition, 371
 nucleophilicity and, 184
steric repulsion, alkenes and, 153
straight-chain alkanes, 126–130
straight-chain alkenes, 114
structures
 benzene, 216–217
 chemical shifts and, 319
 condensed structures, 46–47
 degrees of unsaturation, 144–145
 drawing, 41–42, 45–46, 122
 interpreting tips, 122
 line-bond, 47
 lone pairs on atoms, 51
 names, 120–123
 NMR, IR spectrum and, 308–309
 resonance structures, drawing, 53–63
 solving, 310–318
 as words of organic chemist, 41
studying, success and, 325–326
substituents
 alkenes, 151
 alkyl, Friedel-Crafts alkylation, 233–234
 atoms, hybridizing and, 35
 branching alkanes, 116–118
 complex, naming, 119–120
 curve drawing, 100–101
 definition, 371
 electron-donating, rings and, 237
 electron-withdrawing, 238–241
 meta-directing, 367
 priority, R/S configuration and, 98–99
substitution
 benzenes, 231
 benzenes, synthesis, 241–242
 elimination comparison, 193–194
 first-order, 187–191
 nucleophilic aromatic substitution, 243–245
 rate-determining step, 188
 second-order, 180–187
substitution reactions, 179–180
substrates
 reactions, 194
 S_N1 reaction, 189
 S_N2 reactions, 182–183
success tips
 attitude, 323
 class attendance, 326
 daily practice, 327
 exams, 328
 falling behind, 324–325
 problem working, 323–324
 questions, 327
 studying, 325–326
 tutoring, 326
suffixes
 -ane, 117, 146
 -ene, 146, 169–170
 -yl, 117
 -ylene, 148
 -yne, 169–170

sulfur, degree of unsaturation and, 303
symmetry
 meso compounds, 101–103
 NMR and, 286–287
syn addition, 163, 371
synthesis
 disubstituted benzenes, 236–241
 multistep, problem solving tips, 345–351
 substituted benzenes, 241–242
 Vitamin B_{12}, 347
 Woodward, Robert Burns, 337–338
synthetic organic chemists, 15

• T •

tartaric acid, handedness, 331
tautometers, 371
Teflon
 discovery, 334–335
 introduction, 83
terminal alkynes, 172
termination, reactions, 137–139
tertiary carbocations, alkenes, 156
tertiary cations, alkyl substitutents and, 234
tetravalence, 44
thalidomide, 109
thermodynamic product, 371
thermodynamics
 definition, 371
 kinetics, conjugate addition and, 209
 physical organic chemists and, 17
 thermodynamic product, 208
thiols, 85, 371
thumb technique, chiral center and, 101
ties, alkenes, 151
TMS (tetramethylsilane), NMR and, 285–286
torsional strain, bonding and, 128
totally eclipsed conformation, 129
trans isomer, stability, 152–153
trans stereoisomers
 alkenes, 149
 description, 131
transition state
 definition, 371
 reactions, 182
tree diagram, NMR coupling, 295–296
trigonal planar geometry, bonding and, 32–33
triple bonds
 electronegative atoms, resonance structures, 58
 introduction, 37
 Lewis structure, 43
 resonance structures, 57
triplets, 371
trivalence, 44
tutoring, success and, 326

• U–V •

Undecane, structure, 114
urea synthesis, 330–331

valence electrons
 description, 25
 dots in drawing, 26
 molecular orbitals and, 220
valency of atoms, bonds and, 44
vibrating bonds
 Hooke's law and, 268–269
 IR inactive vibrations, 271
 IR light absorption and, 269–270
Vitamin B_{12}, synthesis, 347
VSEPR Theory (Valence Shell Electron Pair Repulsion), bond geometry, 32–36

• W •

water loss, alcohols (mass spectrometry), 260–261
waypoints, functional groups, 143
wedges, 3D drawing, 94
weigher, mass spectrometer and, 252–253
Williamson ether synthesis, alcohols, 202
willow bark, aspirin, 16
Wittig reaction, alkenes, 154–155
Wöhler, Friedrich, 330–331, 342
Woodward, Robert Burns, 337–338

• X–Y–Z •

-yl, 117
-ylene suffix, 148
-yne suffix, 169–170

Z isomer, 371